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COMMUNICATIONS

TEMPORA MUTANTUR

A NATIONAL scientific journal has many parts to play. Its main duty, of course, is the recording of advances in the subject it professes, and the provision of a means whereby new ideas developed in the country of its origin can be passed into the general circulation of world thought; it should also offer the hospitality of its pages to those workers in other countries who have something to contribute to the general store of knowledge so that the practice of one country can be enriched by the progress of another. But a function of little less importance is to interpret the national spirit so far as the specialty with which it deals is concerned—for each people has its own peculiar means of expression—to nurse this spirit by inspiring its own nationals and to impress it, for what it is worth, on the corporate body of international thought. Moreover, it should foster the desire for enquiry and original observation in its own country and, as a common link and means of expression, bind together the members of the profession into a community with common interests and aspirations.

In these respects the British Journal of Ophthalmology has indeed been fortunate hitherto in those who have guided its policy. Ever since it was founded thirty-two years ago Sir John Herbert Parsons has been the Chairman of its Editorial Committee and our regrets will be shared by all our readers in many lands beyond our shores that he has now vacated his chair. No matter who guides its policy, however, if it is to have any merit and if it is to fulfil its responsibilities, a journal must lean heavily on its editor. To some extent, of course, he is limited by the material presented to him, but the impress of his personality must have a profound influence on the spirit of the publication. For 25 years this Journal has been fortunate in having the services of Robert Rutson James on its Editorial Committee, and for the last 19 years he has occupied the editorial chair. One of the most erudite, and at the same time lovable members of our profession, he has successfully maintained the traditions of the British Journal of Ophthalmology, guiding and encouraging our contributors and impressing his humanity and his unusual geniality upon our pages. Throughout his long tenure of office, he has never spared himself but has laboured faithfully in carrying out his onerous editorial duties, obviously loving everything he has done. It is with regret that we wish these two, who have carried the main responsibility of this Journal for so long, an official farewell; but we who carry their mantle are inspired by their example and comforted in the thought that neither has left us, for we hope they will long be with us to give us help and encouragement.

For the last 19 years Hyla B. Stallard has acted as Assistant Editor of the Journal and has been largely responsible for the technical supervision of its publication. Anyone who is acquainted with the intricacies of periodical publications will understand how fortunate we have been in having the services of one at the same time so able, conscientious and meticulous in everything he undertakes; and everyone who knows him will share our pleasure that he remains upon the Editorial Committee to serve the interests of the Journal in the future.

With the commencement of the thirty-third volume the Editorial Committee has been reconstituted and the Journal finds a new home in the Institute of Ophthalmology in London. Fortunately the new Committee retains most of the members of its predecessor; it thus has the advantage of continuity in maintaining a tradition of which it is proud.

THE RUPTURE OF THE ZONULE IN INTRA-CAPSULAR CATARACT EXTRACTION—A NEW METHOD*†

BY

DANIEL B. KIRBY

NEW YORK

THE rupture of the zonule (zonula Zinnii) of the crystalline lens is the *sine qua non* of intracapsular cataract extraction. It is the purpose of this paper to record some personal observations and experiences and to add them to existing knowledge of the best means of rupturing the zonule in various types of eyes with their different cataracts and zonules. The finding of a fairly large percentage of resistant zonules in the author's surgical experience is accounted for by the fact that the greater proportion of the cataracts operated upon are in the immature stage. In this period, both the capsule and the zonule are more nearly normal and resistant than in mature or hypermature cataracts when both capsule and zonule may be quite fragile. The author's system of intracapsular cataract surgery will be further explained and his new method for direct rupture of the zonule in difficult cases by stripping it from its attachment to the lens capsule will be elaborated upon.

Applied surgical anatomy. The zonule.—The zonule may be defined as the suspensory ligament of the crystalline lens. It consists of homogeneous glass-like fibres covered by a delicate lamella on their anterior surface, taking their origins from the ciliary body, and from the ora serrata where their arrangement undoubtedly accounts for its serrated appearance. The principal fibres run in the ciliary valley and by their early presence and strong formation account for the alternation of ciliary processes and valleys. Termination and insertion is made by the fibres splitting and diverging to fuse with the zonular or most superficial portion of the anterior lens capsule and with the capsule itself in its equatorial portion. In the living, normal eye with the zonule surrounded by aqueous, the lamella being of the same index of refraction as the aqueous, is invisible even with the magnifications possible with the slit-lamp microscope. Only when the eye is opened as in surgery or in the dissection of the fresh specimen is the lamella visible when exposed to the air, and then only when properly illuminated, best with parallel rays of incident light and

* An abstract of this paper was read before the Pan-American Association of Ophthalmology, January 6, 1948.

† Received for publication, March 16, 1948.

viewed with magnification of two or more times. The descriptions of the older anatomists who examined fresh specimens and others who have recently done likewise, rather than those who come to depend upon fixed material, correspond with my clinical surgical observations. The processes of fixation, dehydration, imbedding, sectioning and staining cause the disappearance of the delicate zonular lamella.

The ligamentum hyaloidea capsulare.—Clinically, in intracapsular surgery the ligamentum hyaloidea capsulare does not seem to be more than a coaptation of the hyaloid to the posterior lens capsule, the easiest manoeuvres releasing it. Only in the rare or exceptional case are the hyaloid and the vitreous apparently really adherent to the posterior lens capsule being drawn up in cone shape when the lens is lifted vertically. In the average case, the ligamentum hyaloidea capsulare is easily separated by the manoeuvres directed at the rupture of the zonule and no particular attention need be directed to the former.

Embryology.—The origin of the zonular fibres, at least in the chick embryo, I believe, is in the prolongation of the protoplasmic adhesions which develop when the primary optic vesicle touches the surface ectoderm to stimulate the formation of the lens. After the development of the secondary optic vesicle, the fibres suspend the lens vesicle from the rim of the optic cup. As the ciliary body and iris grow forward from the rim, the fibres are further stretched out and finally in the adult reach between the ora serrata, the ciliary body and the equatorial portion of the lens capsule. The zonular lamella is most probably laid on at the time of the formation of the tertiary vitreous. It is a fallacy that the lens primordium is cast loose into optic vesicle and cup, the zonule being formed later at the time of development of the tertiary vitreous. My observations of the protoplasmic adhesions and the presence of primordial zonular fibres even at the time of the earliest lens formation were made in the course of microdissection of living chick embryos at various ages for the determination of the best age at which the lens might be removed in capsule for pure cultures of lens epithelium *in vitro*.[1] Prior to the time of five days incubation there is not enough space between the pigmented tissues and the lens for separation without leaving pigment cells still attached to the capsule and after five days the zonular fibres become too strong for separation without tearing away pigmented cells or lens capsule. Observations on living embryonic specimens gave me a clearer idea of the origin of the zonule than the study of fixed, stained and cut embryonic material.

The place of the rupture of the zonule.—Observations of cataracts removed in capsule demonstrate that the break in the

zonule is at its union or fusion with the lens capsule. The fibres are the strongest and most important part of the zonule and apparently do not break in twain but separate with a portion of the zonular lamella at the capsule leaving the equatorial portion of the cataract smooth and free from any and all evidence of broken fibre remnants. These findings are contrary to the report of Goldsmith[2] and others, but have been described separately and confirmed by Berliner[3], and others. The clinical observation has also been made that in cases of traumatic subluxation of the lens, there are no microscopic bits or stubs of fibres of the zonule attached to the equator of the lens whereas in congenital subluxation, the defect or coloboma of the zonule is in the region of the ora serrata, the zonular fibres being visible in the area bared by the subluxation of the lens. The separation of the zonule at the capsule accounts for the lack of untoward reaction to surgery of eyes from which the lens has been properly removed in capsule. It also bears out my observation made previously that any pressure used to rupture the zonule should be point pressure or made in the narrow zone of attachment of the zonule to the capsule. Trauma, other than that of traction upon the ciliary body by the lesser zonular fibres, accounts for the development of cyclitis when it does occur after cataract surgery. The relatively low index of the complication of detachment or disinsertion of the retina after intracapsular surgery should calm the fears of those who believe that traction on fibres which took their origin at the zonule might produce separation of the retina.

Various manoeuvres for rupture of the zonule

The manoeuvres designed by various surgeons for rupture of the zonule in intra-capsular surgery are: I. Indirect Rupture by (*a*) Pressure from without, (*b*) Traction on the lens or its capsule and transmitted to the zonule, (*c*) Rotation of the lens in its capsule, (*d*) Various combinations of the above manoeuvres. II. Direct rupture of the zonule used alone or in combination with others of the various manoeuvres described above for indirect rupture to effect delivery by extraction or expression.

The rupture of the zonule is nearly always partial at first and is extended gradually through various forces until it is complete. The most important step in the rupture is the initial one. Some surgeons have one manoeuvre which they try to use in every case, making the eye adapt itself to the manoeuvre. For some eyes almost any manoeuvre is good and sufficient because the zonule is fragile. In case of failure either through inability to rupture the zonule or through rupture of the capsule or untoward immediate or later

effects in the eye itself, the blame is put upon the eye because of lack of adaptability. Rather should the surgeon have all of the above manoeuvres in his surgical armamentarium as his system for rupture of the zonule, and apply the one which is suitable to the particular case. All are valuable alone and in combination. Once started, a rupture may be extended by further procedure, the tear or dehiscence widening and enlarging from the starting point until the lens is freed.

Definitions.—By indirect rupture of the zonule is meant rupture by means of manoeuvres applied through an intermediary tissue, such as the cornea, sclera, lens capsule or vitreous, whereas *direct rupture of the zonule* refers to application of a manoeuvre directly to the zonule by a new method which has proved to be feasible and can be used safely and in a conservative manner under direct visual control when other manoeuvres fail.

The discussion of the various manoeuvres.—It will be well to consider each of the manoeuvres in order to evaluate them, to learn the limits of each in their application, to decide how to apply each to achieve the desired result with the least trauma to the eye, so that prompt graceful healing will supervene and long lasting excellent visual results obtained.

INDIRECT RUPTURE OF THE ZONULE

We will first consider the various manoeuvres producing *indirect rupture of the zonule* separately and together.

PRESSURE

Pressure may be applied directly to the lens or upon the outside of the eye. The ancient surgeons who couched lenses used pressure from within the eye after having pierced the cornea or more frequently the sclera. With a sharp instrument they impaled the lens or with a dull instrument they pressed against the lens forcing it back with the capsule broken or intact in the operation of depression or reclination. Apparently they found then as many resistant zonules as we do now, for when the latter were unyielding they often had to resort to the operation of opening the lens capsule and comminuting the cortex and nucleus, hoping for solution and absorption.

Smith[4] was the greatest exponent of pressure as a means of rupturing the zonule for intracapsular delivery. I believe much can be learned from Smith's work, even though we do not agree that pressure alone is good. Because of anatomical relations, I believe that pressure should be applied by a relatively pointed instrument, as for example the tip of a fine lens expressor hook on

the outside of the cornea. Smith was probably the first to use a strabismus hook for the purpose. I found the tip of the Smith hook too large to be insinuated between the equator of the lens and the ring of the corneal limbus. I have the same objection to other blunt or rounded expressors. I have adapted the hook of Jamison[5] for the purpose, and for ease of manipulation have put a 5 mm. cylindrical handle on it (Fig. 1). After making a superior limbus incision, I selected equidistant points below at 6, 8 and 4 o'clock on *the corneal dial, just inside the ring of the limbus of the* cornea, for the application of pressure. This semi-circular area is directly over the zonule where it joins the lower equator of the lens.

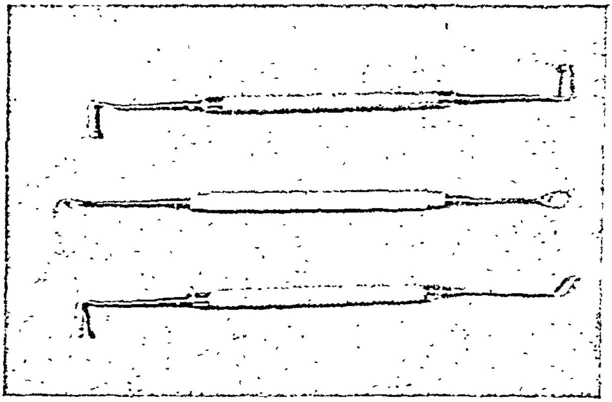

FIG. 1.

Half-size photograph of:—1. Kirby double-ended lens expressor hook. 2. Kirby lens expressor hook with lens loop at opposite end. 3. Kirby lens expressor hook with iris spatula at other end.

The point pressure I have used as an initial procedure before traction or rotation and have applied it in a fairly sudden and sharp fashion, indenting the cornea at the three points 2 to 3 mm., and causing the incision to gape diametrically opposite. Unless contra-indicated, these points may be pressed upon a second time. In some cases, it is evident that a fragile zonule has ruptured below. In such a case, if such pressure were continued, the lens could easily be delivered by expression alone, tumbling out, the hook being insinuated through the cornea back of the lens, following it up in its tumbling manoeuvre and, as it makes its exit, sweeping away the cataract by *stripping off the remaining upper zonule* in all effects the same as Smith described years ago. I have seen a good many cataracts subluxate below in the manner described following the initial pressure, but have had no desire to tumble

them out by pressure alone because it is so easy to pick them up with a suitable forceps[6] and lift them out because of the fragility of the zonules in such cases; and the principle of pressure alone for rupture of the lens in all cases is not a good one. I believe that pressure outside the limbus ring of the cornea is contra-indicated and ill-advised, unnecessary and inefficient, unduly traumatizing, and productive of complications both immediate and late. The use of blunt instruments for pressure is not good because they cover too wide an area, and do not reach the zonule and cause more trauma than necessary.

Point pressure.—The procedure of point pressure, as used by me[7], does not affect rupture of the zonule below in over 15 per cent. of the cases operated upon. It does not rupture the zonule in the average case or in those with resistant zonules. However, if not contra-indicated it gives valuable information, even though rupture of the zonule below is not effected. It reveals the thickness and resistance of the cornea and sclera, the intra-ocular tension or pressure after the incision has been made, the condition of the vitreous, the size and shape and consistency of the cataract and thus permits me, as the surgeon, to judge how best to proceed with the extraction of the cataract.

TRACTION

Traction may be applied prior to the manoeuvre of pressure as Knapp[8] first did with forceps, or it may be applied after or simultaneously within the pressure. I believe the latter most efficient[9]. The manoeuvre of traction may be applied (1) with a loop placed behind the lens, (2) with a pointed hook impaling the lens, (3) with the electro-coagulation electrode of La Carrère[10], (4) with the suction cup either of Dimitry[11] or Bell[12] or the erisphake of Barraquer[13], (5) with the aid of forceps grasping the anterior capsule of the lens.

Traction alone is not a good manoeuvre for rupturing the zonule unless it is applied to certain sections of the zonule at a time. The zonule as a whole is relatively strong and it stands to reason that the zonule as a whole is more resistant than any of its continuous parts. Non-traumatic cataract surgery must be based on a system of a small initial rupture of the zonule being made, this being extended until the whole zonule is ruptured and the lens made free for delivery.

1. *The loop.*—The use of traction by the loop may be indicated when the zonule is partially ruptured, when the loop may be passed through the area of the rupture. It does not seem advisable to use it routinely or to create the initial rupture in the zonule above the loop being passed through it according to the old technique of

Pagenstecher[14] even though he said he could pass it between the posterior capsule and the hyaloid without disturbing the vitreous. Once in place the loop behind the lens, in cases of subluxation, is a good instrument to support the lens and to withdraw it, provided the zonule is fragile, but not so when the zonule is resistant, then it is better judgment to use other manoeuvres as indicated. I have used the loop to bring the subluxated lens into position for use of forceps on the lens capsule and then have used the loop to strip off the portion of the zonule which is still adherent so that the lens may be freed for delivery. If viscid vitreous is anterior to the lens, then the loop is apparently the only safe instrument to use to get the lens into position for extraction. There is hardly any need for a barbed hook or vectis, based on the principle of the points engaging the lens for greater traction.

2. *The pointed hook.*—The pointed hook has been used by some to impale the lens and to draw it from the eye. Those who have done much capsulotomy surgery and have used the cystotome have undoubtedly all had the experience of the lens nucleus being fixed by the point and the zonule when fragile being ruptured and the cataract being withdrawn from the eye. The puncturing of the capsule in this manner will only give a small percentage of deliveries in capsule in the average case even though purposefully applied and it cannot be recommended.

3. *Electro-coagulation electrode.*—The electro-coagulation electrode of La Carrère has been used for changing the protein of the lens cortex and nucleus, causing it to adhere to the electrode and thus permitting the withdrawal of the lens in its capsule. This may be feasible if the zonule is weak, but the procedure can hardly be said to change or weaken the zonule unless it is carried to an unsafe and traumatizing degree. I have had no experience with it.

4. *The suction cup—erisiphake.*—The suction cup of Dimitry or Bell or the erisiphake of Barraquer would be excellent instruments for traction alone, if it were desirable to take up a relatively large portion of the capsule. This would be true if the zonule were always fragile or if it broke as a whole, instead of starting at a small area and then tearing gradually from this beginning. The suction cup is usually applied near the central area of the anterior lens capsule tenting up the entire capsule and zonule if lifted directly up. It is appreciated that in practice the manoeuvres of drawing the cup toward the surgeon as well as of turning the instrument to one side or to the other are feasible, but still the area of capsule affected is too large for easy rupture of the zonule. The instruments are relatively clumsy in their application, take up too much room and do not permit of the application of point pressure, or of rotation or of direct rupture of the zonule by stripping it off

the capsule as adjuvants in the removal of cataracts with resistant zonules. It is true that the suction cup can be applied to the tense or taut and rubbery capsule in certain cases of intumescent cataract when attempts to take up the capsule with forceps fail, but unless the zonule in such cases is found to be fragile, it might be better to release the grasp of the suction cup and to remove some of the fluid from the lens by aspiration as done by Traquair[15] or by point puncture as done by Riddell[16] and then proceed with forceps extraction in capsule. I have not had experience in doing this, but I have opened the capsule and proceeded with the capsulotomy extraction. In some cases where it is evident in the pre-operative examination that the capsule is taut, it has seemed best judgment to permit the cataract to go on to maturity, when it could be handled more gracefully. I appreciate the fact that Barraquer has had success that is admirable, but still the objections as detailed above have been learned in a practical way by others who have tried the use of the suction cup.

The technique of Barraquer includes the principle of traction through the medium of a relatively strong suction effect, which permits considerable direct traction effect with the application of the pressure below and at the side as well as torsional effect combined with pressure through the cornea on the zonule which is under tension, tumbling the lens from one side to the other. The lesser degrees of traction obtainable with the suction syringe of Dimitry or the pipette suction tip of Bell do not afford enough negative pressure to tumble the lens on its vertical axis. Fortunately, it is true that with lesser degrees of suction, the cup will come loose before too much traction is made upon a resistant zonule.

5. *Forceps.*—All surgeons who did capsulotomy extractions, including von Graefe, have most probably had the experience of having the lens coming away in capsule when using toothed capsule forceps designed to remove a segment of the anterior capsule. The teeth have penetrated the relatively thin capsule and have taken a sufficiently firm hold on the hard nucleus to effect with traction the rupture of a fragile zonule.

This happened frequently to Kalt[17], who used his relatively smooth bladed forceps for removal of a section of the capsule, so he purposefully tried to remove the average cataract in its capsule, succeeding in 25 per cent. of the cases. Knapp found no reason to change the model of the Kalt forceps for his intra-capsular cataract surgery and succeeded because he found an efficient method of using them. Various surgeons have devised special forceps. The concave curve of Kalt's forceps[18] adjusts itself to the convexity of the anterior face of the lens and seems best adapted

to get down to grasp the lowermost portion of the capsule. The Elschnig forceps modified by Arruga[19] have been most popular and useful. The Sinclair forceps modified by Castroviejo[20] are of the cross-action type which, when relaxed and closed, hold the grasp of the capsule with a certain pressure, regulated by spring tension which may be adjusted to the desired degree. Arruga forceps blades are well adapted to grasping the area of the capsule just anterior to the supèrior equator of the lens as Verhoeff[21] has done, and it was for this reason that I adopted them.

New intra-capsular forceps.—In developing a new intra-capsular forceps, I combined different features—the length from Kalt, the angle and blades from Arruga, the stops from Verhoeff[22] and have added my own useful cylindrical handle (Figs. 2 and 3). The angle enables one to bring in the instrument from the side and not obscure the field with the hand as in using a straight shafted instrument. I have modified this forceps by using the Kalt concave curve of the shank for special use when I desire to take hold below and tumble the lens. Both of these forceps provide shafts long enough to fit easily into the hand, with cylindrical handles for graceful manipulations. They have the Verhoeff stops, one controlling the opening so that the 4 mm. opening can be adjusted without tension and placed ever so lightly on the lens capsule without pressure and the other controlling the closure so that the blades will not bite out a portion of the capsule unnecessarily. Various cups have been tried and

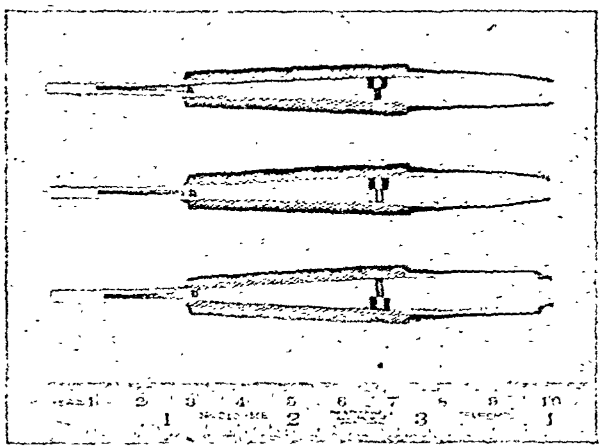

FIG. 2.

Two-third size photograph of:—1. Intracapsular forceps. 2. Iris forceps. 3. Corneo-scleral suture forceps. Front view.

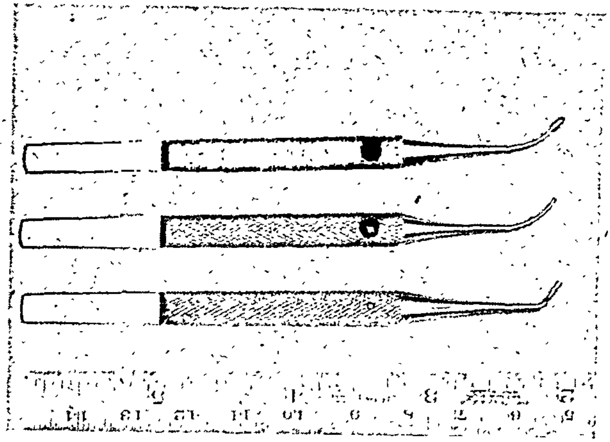

FIG. 3.

Two-third size photograph of:—1. Intracapsular forceps. 2. Iris forceps. 3. Corneo-scleral suture forceps. Side view.

that of Arruga has been selected and incorporated, but it has been offset by 1 mm. from the tip of the curved shank so that it will pick up the capsule only in the relatively small area of the blades and not have the shank behind the blades engage anything else. Such forceps permit the greatest ease of application, manoeuvrability and safety in handling the capsule and affecting various tensions that are purposefully transmitted to small areas of the zonules for simultaneous application and combination with the manoeuvres of pressure, rotation and direct zonulotomy by stripping the zonule from its attachment to the capsule.

Traction as it has been described by various surgeons includes pull tensions made by drawing the capsule vertically, horizontally both forward and transversely, tangentially and diagonally. Forceps are well adapted for the manoeuvres of traction and rotation (Verhoeff described a manoeuvre of " the upper part of the lens swing to and fro laterally with the forceps ").

ROTATION

The manoeuvre is a variation of traction, but is important enough to be considered separately. It causes the lens to turn in the circle of its circumference by traction on the capsule preferably from a point of advantage of grasp just anterior to the true equator of the lens. It is valuable because it puts a tension on the zonule directly surrounding the lens, emphasizing with traction the formation of a tense fold or plica of zonule opposite the point of traction and rotation which may be pressed upon through the

cornea for the greatest rupturing effect with the least effort. The same use of traction and rotation may be made in aiding the manoeuvre of direct rupture of the zonule by stripping it from its attachment to the capsule. There are two other uses for rotation which are valuable. The first is achieved when with the upper half of the zonule ruptured, the application of a second pair of forceps to the lens capsule makes possible further rotation. The zonule below may then be ruptured or torn by wheeling the lens around in the circle of its circumference. The second is the wheel rotation type of delivery rather than the flat sliding delivery, the former offering quite an advantage, there apparently being easier separation of the ligamentum hyaloidea capsulare and less drag on the bared hyaloid or face of the vitreous.

THE APPLICATION OF FORCEPS

Forceps may be applied, except when pressure is inadvisable, simultaneously with pressure from below, causing the lens to tilt, present and be supported by the instrument. Forceps may be (1) applied radially to the capsule below, as far below as can be reached conveniently; (2) to the central area of the capsule; (3) horizontally or vertically to the equatorial region directly above; and (4) to an area just to the right of centre above when the forceps are held in the left hand and *vice versa* when held in the right hand. For a right-handed surgeon it seems easier and more efficient to use the forceps in the left hand and the expressor instrument in the right hand.

1. When the forceps are applied below, the application is radial. It is possible to lift the lens vertically about 2 mm. toward the cornea, horizontally, transversely or cephaled to either side about 3 mm. and about the same diagonally or in rotation. Evidently these movements from the grasp below cause sufficient rupturing action on the zonule, for by the Knapp method with traction alone or by the Knapp[23], Lancaster[24], Torok[25], Stanculeanu[26], Elschnig[27], Arruga[19] and other methods of simultaneous traction and pressure, a large percentage of zonules may be ruptured and the cataracts delivered well and safely by tumbling them out in the capsule. 2. When the capsule is grasped at or near the centre it is apt to cause equal although insufficient tension on the zonule all around the equator. This will result in a lesser percentage of safe deliveries in capsule. 3. The grasp of the capsule tangentially just anterior to the true equator above according to Verhoeff, offers several advantages. (*a*) The surgeon can see better what he is doing, particularly when the corneal flap is lifted. (*b*) He can make localized traction directly away from the nearby zonule. (*c*) He can produce greater tension and direct it to

FIG. 4.

Method of holding and rotating angulated iris spatula with Kirby cylindrical handle.

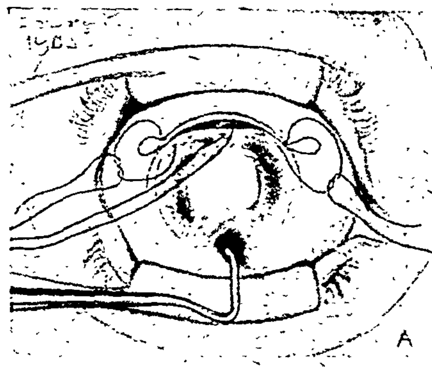

FIG. 5.

First point of preliminary pressure for palpation of the globe and test of fragility of zonule. Note the degree and position of the point of pressure and the effect of gaping of the incision directly opposite. Front view.

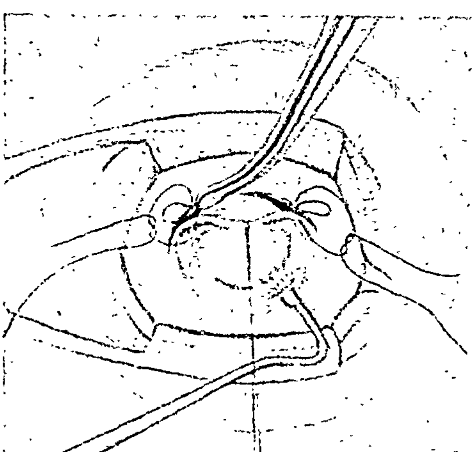

Fig. 6.

The corneal flap is retracted by the suture. Manoeuvre of rotation of the lens to the right, to the 120° meridian with pressure directly opposite at 300° meridian. The zonule is loose nasally. This is one of a series of three illustrations showing the point of pressure and the rotation of the lens Front view

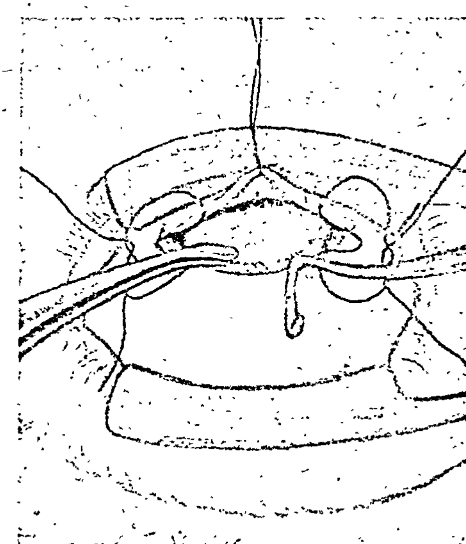

FIG. 7.

Lens rotated to the left and elevated making zonule tense at the left. Application of blunt elbow of lens expressor hook to tensed zonule directly at junction with the capsule for direct separation of the zonule from the equator of the lens. The appearance of the zonule is considerably intensified by the artist. Surgeon's view.

stripped from its attachment to the lens capsule by further use of this manoeuvre. The natural tendency has been to extend the successful use of the procedure to cases in which the cataract does not come away very easily by traction, pressure and rotation. Only in one case which has been reported previously have I had occasion to regret the use of the manoeuvre[29]. (Figs. 4, 5, 6, 7.)

The indications for direct rupture of the zonule

There is no way of determining before the operation that in a certain case a recommended or average degree of pressure or traction should be used, because the individual cases vary and often need more than simple pressure, traction or rotation either applied separately or simultaneously and in combination. The new manoeuvre of direct rupture of the zonule by stripping it from its attachment to the capsule under direct visual control is valuable and should be studied for use when pressure, traction and rotation are insufficient and if when applied to greater degree may be traumatizing. It may also be indicated in cases of subluxation with viscid or fluid vitreous which is in communication with the aqueous of the anterior chamber. The escape of fluid vitreous, directly after the section has been made, causes the intra-ocular tension to fall so low that pressure is of no value at all in the effort to rupture the zonule. The presence of a resistant zonule in congenital or traumatic subluxation requires more than traction with a loop alone for non-traumatic delivery of the lens.

Clinically, in intracapsular surgery the ligamentum hyaloidea capsulare does not seem to be more than a coaptation of the hyaloid to the posterior lens capsule, the easiest manoeuvres releasing it. Only in the rare or exceptional case are the hyaloid and the vitreous apparently really adherent to the posterior lens capsule being drawn up in cone shape when the lens is lifted vertically. In the average case, the ligamentum hyaloidea capsulare is easily separated by the manoeuvres directed at the rupture of the zonule and no particular attention need be directed to the former.

The conditions under which direct rupture of the zonule is safe and practical

These may be stated as (1) the finding of a resilient zonule which resists rupture by the application of pressure, traction and rotation applied simultaneously and in co-ordination. (2) The proper relaxation of surgeon and patient. (3) Proper illumination by parallel beam spot light, extraneous light and glare being excluded. (4) The observation that no undue tensions exist in the eye under operation, there being no gaping of the incision, no prolapse of the iris, no forward position of the lens, hyaloid or

vitreous. (5) The corneal flap should be elevated to afford a direct view of the lens equator which is exposed by retraction of the iris, by removal of blood clots, serum or other fluid, so that the zonule which extends from the equator backward is visible when exposed to the air and viewed with a binocular loupe which affords two power magnification. (6) There should be about 3 mm. distance between the lens equator and the relaxed vitreous and hyaloid. (7) The zonule must be made tense as described to make the manoeuvre easily effective. If all of these conditions are not met, then the manoeuvres should not be attempted. Manipulation, particularly under conditions of poor visibility, may lead to rupture of the hyaloid. In general, it may be said that any surgeon who is acute in observation and does intra-capsular surgery well, should be able to carry out this manoeuvre.

I personally prefer the grasp of the forceps above for the reasons given. If a surgeon has had good success with the radial application of the forceps below, as many have had, he should not be asked to give it up. Cases which are easy or give moderate difficulty with the lower grasp will not be different with the upper grasp, but, when one has a difficult case which resists rupture under these conditions, one may not wish to continue to do that which is ineffective, and one may decide to try the grasp above and to apply the manoeuvres which have been described. Those who use the grasp above need not think that the first grasp with the forceps is the only one which they may take in a particular case. If, for example, it is found that the first grasp is an inefficient one, it may be released and a second one taken, or if in a certain case the first grasp is not near enough to the equator above or below, another one may be taken. Verhoeff has shown that with properly adjusted forceps the grasp may be shifted. In the case of the grasp above, the first forceps may be used to assist in downward traction on the lens capsule for better exposure of the pre-equatorial portion of the capsule.

Results

The results of intra-capsular cataract surgery in my hands during the past fifteen years, in comparison with a previous period of ten years of extra-capsular surgery, justify the continuance of the methods and procedures of the intra-capsular surgery described in this paper. In addition, I may say that the direct rupture of the zonule has been used for ten years. I have had only one occasion to regret its use. It may well be said to be feasible, conservative and desirable where the zonule is found too resistant and difficult to rupture after trial by the other means described.

Summary and conclusions

The rupture of the zonule of the crystalline lens is the *sine qua non* of the intra-capsular cataract extraction. The author has recorded his personal observations and experiences, to add them to the existing knowledge of the best atraumatic means of rupturing the zonule in various types of eyes with their different types of cataracts and zonules. The findings of a fairly large percentage of resistant zonules, in the author's surgical experience, is accounted for by the fact that the greater proportion of the cataracts operated upon are in the immature stage. In this period, both the capsule and the zonule are more nearly normal and resistant to rupture than in mature or hypermature cataracts, when both capsule and zonule may be quite fragile.

In observations of the applied anatomy during clinical surgery the zonule is observed as a lamella covering the fibres. The zonule is visible when exposed to the air and viewed with two power magnification. Dissections of early chick embryos brought out the finding that the zonular fibres may well be formed through elongations of protoplasmic adhesions established at the time of contact of the optic vesicle with lens ectoderm. The lamella may be added at the time of the formation of the tertiary vitreous.

The zonule usually ruptures in a small area first and gradually the entire zonule is separated. The place of rupture of the zonule is always at its union with the lens capsule. The latter is smooth after intra-capsular extraction.

The various manoeuvres for rupture of the zonule may be found classed under I, *Indirect rupture* (*a*) pressure from outside the globe, (*b*) traction on the lens or its capsule and transmitted to the zonule. This includes rotation of the lens in its capsule, (*c*) various combinations of these manoeuvres. II, *Direct rupture* of the zonule used alone or in combination with the various manoeuvres which cause indirect rupture.

Each of these manoeuvres is considered alone and in combination with others. The principles underlying the classical and well known operations of various authors are explained. Pressure alone may be found to rupture fragile zonules, but traction is preferred for delivery even in such cases. A combination of pressure and traction is more efficient than either alone. Rotation of the lens in its capsule is used particularly to produce conditions whereby pressure and traction may be co-ordinated to produce the greatest effect with the least effort. The method of shifting the grasp of the forceps or the use of a second pair of forceps to provide greater rotation when necessary is given.

The reasons for the preference of the grasp of forceps over that of the suction cup or the use of the loop or spoon are given.

Rotational delivery is preferred to the direct sliding or the tumbling methods.

The new method of feasible and practical direct rupture of the zonule by separating or stripping it from its attachment to the equatorial lens capsule has been partially considered and reported before. To the present date, the author has not found any similar method in the literature. The indications for its use, the determination of the cases in which resistance of the zonule is found, and the conditions under which direct rupture of the zonule may be applied successfully without injury to the hyaloid, presentation or loss of vitreous are given.

The author prefers the grasp of the forceps above for various reasons. If many others have had success with the grasp below, there is no need for them to change. But, if a difficult case is encountered, the grasp of the forceps may be shifted above and the manoeuvres, as described, may be tried. Those who use the upper grasp may find that they may shift the grasp above to one nearer the superior equator if necessary. A second pair of forceps may assist in this in drawing down the pre-equatorial capsule. The author reports the further application of the procedure as desirable, feasible and practical in difficult cases of cataract with resistant zonules. A follow-up of the cases in which this manoeuvre has been applied in a period of five years has proved that there has been no undue reaction, inflammation or infection, that the eyes have done well and that there has been good healing with good visual results.

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STUDIES ON THE INTRA-OCULAR FLUIDS*

1.—The Reducing Substances in the Aqueous Humour and Vitreous Body

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IN a recent paper to this Journal (Duke-Elder and Davson, 1948) a general review of the present position of our knowledge regarding the nature of the intra-ocular fluids was given; the present paper deals more particularly with our experimental work on the reducing substances (sugars, etc.) in the aqueous humour and the vitreous body. It has long been recognized that the concentration

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of reducing substances in the aqueous humour is low in comparison with that in the blood plasma (Adler, 1930; O'Brien and Salit, 1931) and the concentration in the vitreous body is still smaller. This has received three explanations.

(1) The low concentration in the ocular fluids has been ascribed to secretory activity. In view of the metabolic importance of glucose, however, it seems doubtful from a teleological standpoint whether a secretory system would be evolved providing a smaller concentration of this substance than can be produced by a simple mechanical process of filtration. Moreover, the site of such a secretion would presumably be the ciliary epithelium; and the secreted fluid, diffusing from this region through the pupil, would be available to both vitreous body and the anterior chamber so that we should not expect the concentrations in the two compartments of the eye to be significantly different: such a difference, as we shall see, occurs.

(2) Assuming that the aqueous humour is formed, at least partly, by a process of ultra-filtration whereby proteins are left behind to give a comparatively protein-free fluid, if a substance finds some difficulty in passing the barrier between the blood and the cavity of the eye but at the same time can find a free exit, it will be in a deficiency in the aqueous humour in comparison with the blood (Kinsey and Grant, 1942). In this view, the low concentration of glucose would be evidence not of a secretory mechanism in respect to this substance, but rather of the existence of a filtration process.

The mathematical formulation of the problem as set out by these authors has been criticised by us (Duke-Elder and Davson, 1944), and ~~recently~~ Palm (1948) has suggested an equation that promises to reconcile the opposing standpoints.] We need not confuse the issue in this paper by introducing a mathematical discussion; it is sufficient to state that the effect postulated by Kinsey and Grant is a feasible one, but that it will depend to a great extent on the rate of penetration of the substance concerned. If the substance penetrates slowly and with difficulty, we may expect to find a deficiency of it in the aqueous humour when the steady state is achieved simply because it is drained away too rapidly to be adequately replaced. If the rate of penetration is comparatively rapid, on the other hand, as with ethyl alcohol (Palm, 1948), the effect will be negligibly small. The much lower concentration of glucose in the vitreous body, however, would be difficult to explain on a simple kinetic basis, especially since no flow through this structure has so far been demonstrated.

(3) A third explanation ascribes the deficiency of glucose to its absorption in the metabolic needs of the lens and retina. The lens

utilises glucose and this must clearly be derived from the aqueous humour and the vitreous body; as the glucose is abstracted from these sources more will diffuse through the blood-aqueous barrier to replace that used up, but since this diffusion process must wait on the utilisation of the sugar to cause the necessary concentration gradient, we must expect a steady state to be established with the concentration lower in the aqueous humour than in the blood plasma. In the case of the posterior cavity of the eye containing the vitreous body, we might not expect to find any greater deficiency since, although this structure is in apposition to the retina which consumes glucose at a great rate, the latter is directly supplied by blood from the capillaries of both the uveal and retinal circulations; there seems little reason why the vitreous body should be involved in this respect. If we assume, however, that the vitreous body receives its glucose, not exclusively by diffusion or secretion from the ciliary body, but rather by diffusion from the capillaries of the retinal and choroidal circulations, then the fact that these capillaries are supplying large quantities of glucose to the retina must influence the concentration in the plasma available for diffusion into the vitreous body. In other words the transudate derived from the choriocapillaris and retinal capillaries is so depleted of sugar that the available concentration for diffusion into the vitreous body is low.

In the present paper it will be shown that the low concentration of glucose in the intra-ocular fluids is predominantly, if not exclusively, a result of the metabolic factors discussed above.

EXPERIMENTAL

Static Studies. Great care was taken to avoid the hyperglycaemia associated with fear in the experimental animals; nembutal was used as anaesthetic, intraperitoneally in the cat and intravenously in the rabbit. In the latter animal it is impossible to avoid hyperglycaemia, and before fluids were removed the animal was "equilibrated" for some hours with its head projecting from a bleeding-box. For comparison of normal and aphakic eyes this equilibration was not so important and was generally omitted. Blood was withdrawn from the cat by arterial puncture, and from the marginal ear vein of the rabbit after vaso-dilatation with toluene. Sugars were determined in duplicate by the Hagedorn-Jensen technique (1923) on Somogyi (1930) filtrates of the various fluids; sucrose was determined by estimating the reducing value of the fluid before and after hydrolysis in 0·1 N H_2SO_4 (15 min. at 100° C.). The difference between duplicates rarely exceeded ·1%, except if the reducing value was low, when it amounted to 2%. Removal of the lens was carried out by the standard surgical procedure for extracapsular extraction. (Intracapsular extraction is impossible in these animals owing to the adherence of the vitreous to the posterior lens capsule.)

Dynamic Studies. The general principle was to maintain a constant high level of a given sugar in the blood by continuous intravenous infusion of an isotonic solution in 6% gum acacia under nembutal anaesthesia. Rapid elimination of the injected sugar was prevented by tying the renal arteries. One eye was, in general, removed before the injection, to estimate the initial reducing value of the intraocular fluids, and the other after a known time interval. With sucrose, which is

estimated independently of the reducing substances in the fluids, the preliminary removal of one eye is unnecessary. After enucleation, the aqueous humour was withdrawn and the eye was then frozen in solid CO_2. When hard, the eye was cut into two or more pieces as described later; the frozen pieces of vitreous body were filtered through glass-wool as they melted in order to break down the gel structure. Blood and aqueous humour were immediately placed in tubes surrounded with ice.

RESULTS

1. STATIC STUDIES: THE CONCENTRATION OF REDUCING SUBSTANCES.

(a) *The normal distribution.*

The concentrations of glucose in the aqueous humour, vitreous body, and blood plasma of rabbits and cats are shown in Table I.

TABLE I

GLUCOSE CONCENTRATIONS (MG./100G.H_2O) IN PLASMA AND Aqueous INTRA-OCULAR FLUIDS

	Plasma	Fluid		R_A=aq./pl.	R_V=vitr./pl.
		Aqueous	Vitreous		
Rabbit	131	116	56	0·89	0·425
	133	118	66	0·89	0·495
	142	110	74	0·78	0·52
	149	128	87	0·86	0·58
	160	134	73	0·84	0·46
	163	145	82	0·89	0·50
Mean	—	—	—	0·86	0·49
Cat	125	95	64	0·76	0·51
	89	73	55	0·82	0·615
	92	78	52	0·85	0·565
	119	86	61	0·72	0·51
	104	67	44	0·64	0·425
	121	89	58	0·74	0·48
	103	89	64	0·87	0·62
Mean	—	—	—	0·77	0·53

It is seen that the concentration of glucose in the aqueous is less than that in the plasma by some 15 to 20%, while that in the vitreous is still less, being approximately half that in the plasma. The results on the cat amply confirm those of Adler (1930); the low glucose content of the vitreous body is striking.

(b) *Distribution in the aphakic eye.*

There are two main loci of sugar utilization in the eye—the lens

and retina. That the lens modifies the sugar content of both the aqueous and vitreous humours is shown in Table II in which some typical results on rabbits and cats are presented. The lens

TABLE II

GLUCOSE CONCENTRATIONS (MG./100 G. H_2O) IN FLUIDS OF NORMAL AND APHAKIC EYES

	Interval after extraction (weeks)	Plasma	Fluid			
			Normal aqueous	Aphakic aqueous	Normal vitreous	Aphakic vitreous
Cat No. 1	4	89	64·5	83	—	—
	6	98	72	83	—	—
Cat No. 2	7	88	66·5	81	—	—
	9	104	66·5	83	44	57
Cat No. 3	3	95	76	81	—	—
	4	—	74	81	—	—
	6	88	76	82	45	53
Rabbit No. 1	3	214	165	149	—	—
	5	183	127	99	—	—
	6	185	166	147	—	—
	7	208	157	129	99	107
Rabbit No. 2	3	161	152	145	—	—
	5	126	103	105	—	—
	6	145	126	121	—	—
	7	178	162	158	99	111
Mean (9 rabbits)	7/14 weeks	152	124	117	87	96

was removed from one eye, and at various intervals after the operation, when the eye had quietened down, aqueous humour was withdrawn from both; finally, both eyes were enucleated. In the cat, the increase in the concentration in the aqueous humour after extraction of the lens was pronounced (20% or more) in two cases, whilst in the rabbit it was much smaller; in fact, there may be an actual decrease, as in rabbit No. 1. This seems to be due to diffusion backwards through the pupil into the vitreous body, since rabbit No. 1, in which this effect was most marked, had a wide iridectomy and dilated pupil, whereas rabbit No. 2 had no iridectomy, a constricted pupil and some opaque lens matter partially covered the pupillary aperture. Similarly cats Nos. 1 and 2 had portions of opaque lens material remaining in the pupil, whilst in cat No. 3 the pupil was wide and completely unobstructed. The mean for nine rabbits shows a 6% decrease in the aqueous humour in the aphakic eye. The vitreous body showed a

large increase in the cat (30%) and a smaller increase in the rabbit. It is to be remembered, however, that the normal eye of the rabbit contains a higher concentration of ascorbic acid than the aphakic eye (Goldman and Buschke, 1935) and, since this substance contributes to the reducing value of the aqueous humour, and is therefore included in the estimations, the increase in the concentration of glucose in aphakia in this animal is partially masked by the decrease in the concentration of ascorbic acid.

The fact that the fluids of the aphakic eye do not show sugar concentrations equal to that in plasma suggests that the retina is utilizing glucose. If glucose is consumed by the retina of the enucleated eye, the concentration of glucose after incubation should be less in the periphery than in the centre of the vitreous body.

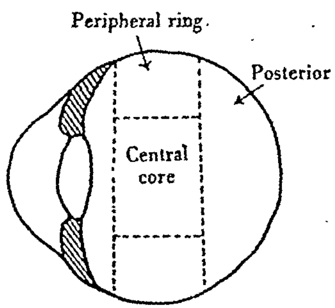

FIG. 1.

Sectioning of the frozen vitreous before and after incubation.

(*c*) *Concentration in the incubated excised eye.*

The two eyes of a cat were removed; one was frozen immediately, while the other was placed in a boiling tube in the bottom of which there was cotton-wool moistened with 0·9% NaCl; the tube was immersed in a bath at 38-40° C. After 2 hrs. the eye was frozen. The eyes were sectioned as indicated in Fig. 1, giving a large central disk and a thinner posterior cap of vitreous body. With a cork-borer the central disk was divided into a core and peripheral ring, the latter about 3 mm. wide. The *differences* in the glucose contents of the aqueous humour and of the various parts of the vitreous body *before and after incubation* were as follows:

		GLUCOSE DIFFERENCE mg./100 g.
Vitreous body	Core of central disk	15
	Periphery of central disk	40
	Posterior cap	30
Aqueous humour	—	27

The result leaves little doubt that the retina is responsible for at least a part of the consumption of glucose in the posterior cavity of the eye. If the lens only were consuming glucose, the core of the central disk would have shown the greatest loss since it was in immediate contact with the lens; on the other hand, the greatest loss is in the peripheral regions next to the retina.

In the eye, immediately after enucleation, the glucose is apparently not uniformly distributed through the vitreous body: Adler (1930) has shown that in the frozen eye the anterior half of the vitreous body contains more sugar than the posterior. In a series of nine rabbits we have found that if the middle disk (Fig. 1 (a)) of the frozen vitreous body was divided into a central core and a peripheral ring, the latter invariably contained the higher glucose concentration. It is possible that these differences in concentration are, at least in part, artefacts resulting from the freezing process, so that it is not justifiable to draw definite conclusions from the observed concentrations regarding the relative extents to which glucose is utilized in the different parts of the eye. The finding of a lower concentration in the central core is, however, reasonable, since it is in immediate contact with the lens. On incubation, however, this relationship is invariably reversed, both in the cat and rabbit; in these circumstances we must assume that the retina draws on the glucose in the vitreous body owing to the absence of the retinal and uveal circulations.

(*d*) *Concentration in mydriasis and miosis.*

A series of experiments were done to determine the concentration of reducing substances in the aqueous humour in mydriasis and miosis. One eye of a cat was treated with eserine and the other with atropine; after about 2 hrs. the aqueous humours were withdrawn from both eyes. The mean results for four cats (two of them kittens) were as follows:

	Glucose mg./100 g.
Atropinized eye	70
Eserinized eye	75
Plasma	107

This rise in the concentration of reducing substances in miosis may, in part, be considered due to a reduction of the area of lens exposed to the aqueous humour. Alternatively, eserine, by breaking down the blood-aqueous barrier, and by increasing the dialysing surface of the iris, may permit a readier penetration of glucose from the blood. It is to be noted that if glucose reaches the anterior chamber by way of a flow from the posterior chamber through the pupil, miosis should restrict this flow and so produce a lower concentration.

(e) Concentration in the plasmoid aqueous.

Again, it may be expected that the aqueous humour formed immediately after the emptying of the anterior chamber (paracentesis) should have a higher concentration of glucose, since the lens will not have had time to re-establish a steady state. The results of a typical experiment are as follows, the 'second' re-formed aqueous humour being the fluid formed after the successive withdrawals of the original and 'first' re-formed aqueous humour:

	Glucose mg./100 g. H_2O
Normal aqueous humour	62·5
First re-formed humour	83·5
Second re-formed humour	85·5
Plasma	89

In no instance, however, did the glucose concentration in the re-formed fluid equal that in the plasma.

2. KINETIC STUDIES: THE RATE OF ENTRY OF REDUCING SUBSTANCES.

The permeability of the membranes of the eye to the following sugars was investigated: glucose, galactose, 3-methyl glucose, xylose and sucrose. 3-methyl glucose is a synthetic compound which is apparently not phosphorylated *in vivo* (Campbell, unpublished) and was thought, on this account, to be unlikely to be secreted.

Detailed results of seven experiments with glucose are presented in Table III in order that the animal-to-animal variations may be appreciated. Constants indicating the rate of penetration into both aqueous humour (K_A) and vitreous body (K_V) have been calculated in accordance with the equation of Davson and Quilliam (1940).*

Owing to the impossibility of obtaining large supplies of xylose no more than six experiments could be carried out; consequently Student's '*t-test*' for the differences between means of small samples was applied successively to the mean values of K_A/K_V for xylose and the individual hexoses; the values of P_S (Yule and Kendall, 1940), indicating the probability that the values of *t* so computed would occur by chance, are included in the table. With 3-methyl glucose and galactose the differences in the ratios are significant; with glucose, where greater variability was encountered, the difference is not significant. The large increase of the ratio K_A/K_V on passing to the disaccharide is clearly significant.

* The equation is only approximate owing to the utilization of sugar by the eye, but in view of the large animal-to-animal variations refinements seem unnecessary. When the plasma reducing value is raised by several hundred per cent. the steady state finally achieved tends to equality of concentration expressed as mg./100 ml. as opposed to mg./100 g. H_2O (*i.e.*, the true concentration in the plasma is about 7% higher than in the aqueous humour), and for this reason the former unit has been used in these kinetic studies.

TABLE III

THE RATE OF PENETRATION OF GLUCOSE INTO THE AQUEOUS HUMOUR AND VITREOUS BODY OF THE CAT

Plasma (mg./100 ml.)	Aqueous (mg./100 ml.) A_1	Aqueous (mg./100 ml.) A_2	Time (hr.)	$100K_A$	$100K_V$	K_A/K_V
280	94	254	2.0	38	11	3.45
290	140	188	0.5	33	16.5	2.0
265	92.5	144	0.75	20.5	12	1.7
266	130	232	2.0	30	10	3.0
280	104	202	0.62	57	7	8.1
597	112	238	0.47	31	10	3.1
439	88	233	0.75	30.5	9	3.4
Mean	—	—	—	34	11	3.1

In the above table A_1 is the initial concentration in the aqueous humour; A_2 the concentration in the aqueous humour after the blood concentration, P had been maintained for t hours. K_A is given by the equation:

$$K_A = \frac{kA}{V} \times \frac{1}{2 \cdot 303} = \frac{1}{t} \log \frac{P - A_1}{P - A_2}$$

where k is the true permeability constant, and A and V are the area and volume of the system respectively. K_V represents a similar constant derived from the concentrations in the vitreous body.

TABLE IV

PENETRATION OF DIFFERENT SUGARS INTO THE EYE FLUIDS OF CATS

Sugar	No of cats	$100K_A$	$100K_V$	K_A/K_V	P_S
Xylose	6	37 ±2·7	16·5 ±1·5	2·2	—
Glucose	7	34 ±2·2	11 ±0·8	3·1	0·125
Galactose	9	33·5 ±2·3	9·5 ±0·9	3·5	0·006
3-Methyl glucose	5	36·5 ±2·9	11 ±0·5	3·3	0·02
Sucrose	9	4·9 ±0·6	0·29 ±0·05	17	—

K_A and K_V have the same meaning as for Table 3. P_S is the probability that the value of Student's t, computed from the mean xylose K_A/K_V and the hexose K_A/K_V, would occur by chance (Yule and Kendall, 1940). Standard errors are also shown.

Table III shows a consistent difference in rates of penetration into the aqueous humour and vitreous body, the rate for the aqueous humour being some three times greater. In Table IV the results for the remaining sugars are presented in the form of the constants, K_A and K_V only. The following points may be noted:

(*a*) The rates of penetration of monosaccharides, whether pentoses (xylose) or hexoses into the aqueous humour are not significantly different; the disaccharide, sucrose, on the other hand, penetrates very much more slowly.

(*b*) The rates of penetration of the monosaccharides into the vitreous body show a significant difference. The pentose, xylose, shows the most rapid entry, a little over one-half its rate of penetration into the anterior chamber ($K_A/K_V=2{\cdot}2$). The rates of penetration of the hexoses are all of the same order—about one-third of those into the aqueous humour ($K_A/K_V=3{\cdot}1$ to $3{\cdot}5$). In the case of sucrose, penetration is very small indeed; the factor is one-seventeenth ($K_A/K_V=17$).

The results suggest that *the barrier separating the blood plasma from the vitreous body is more selective than that separating it from the aqueous humour;* thus the latter apparently does not discriminate between a hexose and pentose, whereas the former appears to do so; as the molecular size is increased the greater selectivity of the barrier separating the vitreous body from the blood is shown in the increasing value of K_A/K_V.

The Site of Entry. The differing relative values of K_A and K_V for any given sugar suggest that this substance can enter the eye from other regions than the ciliary body; if penetration took place only from the ciliary body it would be expected that, after maintaining the blood sugar level at a high value for (say) an hour,

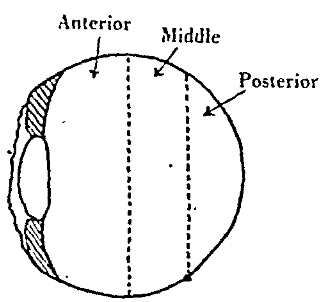

FIG. 2.

Sectioning of the frozen vitreous body before and after diffusion experiments, the aqueous humour having been removed.

the concentration in the part of the vitreous body most remote from the ciliary body would be smaller than in that nearest. In thirteen different experiments, the eyes, after removal of the aqueous humours, and freezing, were cut approximately as in Fig. 2; these gave as mean volumes for the various sections:

posterior, 0·35 ml., middle, 0·43 ml., and anterior, 0·63 ml. The different parts were analysed and the results are shown in Table V. It will be seen that, for the control eyes, the mean concentration in the middle section was 67 mg./100 g. H_2O, being 92% of that in the posterior section; after a high blood-sugar had been

TABLE V

CONCENTRATIONS OF SUGAR (MG./100 G. H_2O) IN THREE SECTIONS OF VITREOUS BODY AFTER MAINTAINING A HIGH BLOOD CONCENTRATION FOR A DEFINITE PERIOD, COMPARED WITH THE CONCENTRATION IN THE CONTROL EYE. MEAN RESULTS OF THIRTEEN EXPERIMENTS

	Section of vitreous body		
	Posterior	Middle	Anterior
Control	73	67	75
Test	124	98	113

maintained for about 1 hr. the average concentration in the middle section was 98 mg./100 g. H_2O, being only 78.5% of that in the posterior section. The results certainly suggest that *the locus of diffusion into the vitreous body is not confined to the ciliary body*, but occurs throughout the whole posterior segment of the eye. It must be remembered, however, that deductions from the concentrations of dissolved material in the frozen eye are to be accepted with caution. To minimize any such fallacy, conditions of freezing were kept as uniform as possible so that disturbances in distribution would operate to the same extent in the control and test eyes, and it would seem that the results are significant.

These results prompted an inquiry into the site of entry of substances into the aqueous humour; if diffusion takes place entirely from the ciliary body, they must enter the anterior chamber through the pupil; and a variation in the size of the latter might modify the rate of appearance. Diffusion experiments were carried out as before, but one eye of the cat was eserinized and the other atropinized. If diffusion takes place only from the ciliary body the rate of entry should be less in the eserinized eye with its extremely narrow slit-like pupil. The results are shown in Table VI and confirm those in the concentration experiments previously recorded; invariably the rate of entry of sugar into the eserinized eye was more rapid than into the atropinized eye.

These results strongly suggest that the primary effect of eserine on the penetration of sugars into the eye is to diminish any block to the passage of sugar presented by the blood-aqueous barrier

TABLE VI

THE RELATIVE RATES OF ENTRY OF SUGARS INTO ATROPINIZED AND ESERINIZED EYES

Sugar	Time (min)	Atropinized eye	Eserinized eye
Galactose	40	152	214
Galactose	27	215	239
Glucose	60	242	257
Xylose	41	191	199
Galactose }	62	150	164
Sucrose }		18	28
Sucrose	110	38	51

The figures represent sugar concentration in the aqueous humour, in mg./100 g. H_2O, after maintaining a high sugar concentration in the blood for a given time.

(as, for example, by inducing vaso-dilatation) and/or to increase the area across which passage is possible (the surface of the iris). If such were its effect, we should expect the influence of the drug to be greater proportionately on a substance that penetrates the barrier with difficulty. The bracketed results in Table 6, which describe the effect of eserine on the penetration of both galactose (penetrating comparatively easily) and sucrose (penetrating with difficulty) show that this effect is clearly much stronger with the latter substance. On purely mechanical grounds we should expect a less ready flow of aqueous humour through the pupil when the latter is a mere slit, and the fact that sugars actually penetrate into the anterior chamber at a faster rate would suggest either that flow through the pupil is not affected by its size or that the partial breakdown of the blood-aqueous barrier or an increase in its area obscures any effect of diminished flow.

Discussion

There seems little doubt from the results of the first part of this paper that metabolic factors play an important part in determining the low concentration of reducing substances in the intra-ocular fluids. The influence of the lens is seen in the higher concentration in aphakic eyes; but in these the aqueous humour and plasma levels still differ by a factor of some 10% in the cat.

From the observed concentrations and the constant, K_A for glucose, it is possible to calculate the rate of absorption of glucose from the anterior chamber; it amounts to about 0·15 mg./hr., a figure not inconsistent with the known sugar utilization of the

lens (Kronfeld and Bothman, 1928). From the posterior cavity of the eye the lens and retina may both extract glucose, and the concentration in the vitreous body is therefore less than in the aqueous humour. The regional distribution of glucose in the vitreous body is explained by this dual consumption. The aqueous humour immediately re-formed after paracentesis has a glucose concentration differing by only about 5% from that of plasma; here the effects of the activity of the lens and diffusion through the pupil are minimized, and one might expect to find the concentrations equal. Three factors, however, must be taken into consideration. In the first place, a small fraction of the sugar in the blood is probably bound to the proteins of the plasma and is therefore not free to diffuse across a membrane impermeable to protein. In the second place, the blood used for comparison was arterial; the eye is an organ with a very high metabolism and we may therefore expect an arterio-venous difference in sugar concentration. It is to be remembered that differences as large as 39 mg./100 g. between the blood-sugar content of the carotid artery and vortex vein have been reported; the greater portion of this discrepancy is probably due, however, to activity in the more posterior parts of the eye. The glucose concentration in the capillary plasma is almost certainly, on the average, less than that in arterial plasma. Finally, the non-sugar reducing substances in the plasma represent a considerable fraction of the whole (27 mg./100 ml. according to Somogyi, 1927); the membrane separating the aqueous humour from the plasma has a high degree of selectivity in respect to nitrogenous compounds (unpublished) and it is possible that the re-formed aqueous humour, formed by a rapid process of ultra-filtration and therefore not necessarily equivalent to a dialysate, contains a lower concentration of non-sugar reducing substances than would be the case if time were permitted for dialysis to proceed to completion. The behaviour of sucrose is a case in point; if a high sucrose concentration is maintained in the blood of the cat, it is found that the re-formed aqueous humour after paracentesis has a sucrose concentration only 60% of that in the blood.

This consideration brings us to the viewpoint put forward by Kinsey and Grant (1942); according to their treatment, the deficiency of glucose in the aqueous humour is due to the difficulty of entry of this molecule during a filtration process and the freedom of its exit in the drainage of aqueous humour from the anterior chamber. That such a retention is theoretically feasible we have indicated in the introduction to this paper and is moreover confirmed by the experiment on sucrose described above; sucrose, however, penetrates the eye with great difficulty, whereas glucose enters at a rate some seven times greater. Without an exact mathematical analysis, which so far has not been made owing to the difficulty in assessing one of the parameters in the process, it is not possible to state on theoretical grounds whether the effect of this retention will manifest itself measurably in respect to glucose. As we have indicated earlier, we have some evidence that

when the blood sugar level is raised considerably, so that metabolic consumption becomes proportionately less significant, glucose penetrates the eye and approaches a steady state in which the concentration, expressed as mg. 100 g. H_2O, is some 7% lower than in the plasma. This suggests that the effect of retention is measurable in the case of glucose, but that it is by no means sufficient to account for the 23% difference pertaining in the normal animal.

It is difficult to assess experimentally the true steady-state with glucose since a high blood sugar concentration must be maintained over a period of hours; and during the last hour this concentration must be kept constant. The matter is further complicated by the non-specificity of the usual methods for determining sugars. So far as the aqueous humour is concerned, therefore, we may say that the low concentration of glucose is due mainly, if not entirely, to metabolic factors; the retention factor of Kinsey and Grant, whereas it probably plays an important rôle in the steady-state achieved by sucrose and other substances penetrating more slowly, is not the determining factor with respect to glucose.

With urea, on the other hand, it would seem that for the low concentration, described first by Adler (1933), and later confirmed by a number of authors and also in our laboratory, the explanation of Kinsey and Grant is at least theoretically valid; urea penetrates at less than half the rate of glucose (Davson, Duke-Elder, Maurice, Ross and Woodin, 1949), and here metabolic influences may be ruled out.

The kinetic studies tend to confirm this view of the steady-state; the barrier between the plasma and the aqueous humour shows no special selectivity towards glucose but permits galactose, the synthetic 3-methyl glucose, and the pentose, xylose, to pass at about the same rate. If any secretory activity were involved, one might expect, by analogy with intestinal absorption, to find appreciable differences in rates, particularly in the case of the synthetic sugar which we might not expect to be secreted at all and certainly not at the same rate as glucose. The slow rate of penetration of sucrose is in agreement with some earlier preliminary work on the dog (Weld, Feindel and Davson, 1942) in which it was shown that this molecule represents the limiting size for sugar penetration, the trisaccharide, raffinose, hardly penetrating at all. So far as these results go, it would appear that a purely physical explanation of diffusion depending on molecular size, meets the case.

The striking difference in selectivity between the barriers separating the aqueous humour and vitreous body from the blood is of some significance; hitherto it has been considered sufficient, in the interpretation of intra-ocular dynamics, to study the penetration of substances into the aqueous humour only. The existence of this more selective membrane lining the posterior cavity of the eye may well mean that the composition of the vitreous body plays a part of some importance in the determination of the intra-ocular pressure: if there is any secretion into the eye

it will obviously be more effective in modifying any difference between the osmotic pressures of the ocular fluid and plasma if the secreted substance does not leak away rapidly.

The question may reasonably be raised whether the differences in K_A and K_V represent actual differences in permeability constants. The constants K_A and K_V contain the factor A/V, the ratio of area of membrane to volume of fluid, and if this is not the same for the two compartments of the eye the constants are not directly comparable. In the cat, the volumes of aqueous humour and vitreous body are roughly in the ratio of 1 : 1·5, but it is impossible to state the effective areas of membrane; in view of the large number of ciliary processes, it would appear that the area available for diffusion into the vitreous body is considerably the greater, in which case the difference between the true permeability constants would be greater still. It is not necessary, however, to know the values of A/V in determining whether the differences in K_A and K_V represent differences in permeability constants; if the membranes had identical characteristics we should expect the ratio K_A/K_V to be the same for different molecules; as we have seen, this is by no means true for the ratio increases with increasing size of molecule. In a similar way, the effects of different viscosity and different rates of mixing in the two fluids should manifest themselves to approximately the same extent for different molecules.

It is of interest to assess the actual value of k, the true permeability constant for hexoses, from an assumed area-to-volume relationship. k is given by:

$$k = \frac{KV}{A} \times 2{\cdot}3 \text{ (Davson and Quilliam, 1940).}$$

Conventionally, k is expressed as the number of g.-mol. of the substance penetrating $1\mu^2$ of surface in 1 sec. when the concentration difference is 1 mol./1. If the volume of the aqueous humour is taken as 1 ml. and the diffusing surface as 1 cm.^{2}, k comes out at approximately 2×10^{-15}. This compares with a value of $7{\cdot}8 \times 10^{-16}$ for the penetration of urea into the ox erythrocyte, an instance of high permeability. The effective area of diffusing surface for the anterior chamber is, of course, likely to be very much higher than 1 cm.^{2}; if the area-to-volume relationship were comparable with that in the erythrocyte where 1 ml. of cells has an area of about $1 \times 10^{12}\mu^2$ (Ponder, 1934), k becomes 2×10^{-19}. Such an extreme instance of area-to-volume relationship is unlikely to apply to the eye, but even this value of k suggests that the rate of penetration is comparatively high when it is appreciated that the penetration of the smaller molecule, erythritol, into plant cells gives constants ranging from 7×10^{-21} to $1{\cdot}3 \times 10^{-19}$ (*vide* Davson and Danielli, 1943).

It therefore seems likely that the penetration of hexoses into the eye is a rapid permeability process; this fact, and the absence of a significant difference in rate between hexoses and the pentose, might suggest a penetration by way of water-filled pores, *e.g.*, through the intercellular spaces of the iris capillaries and iris endothelium. Evidence derived from a study of the penetration of some other substances, however, is against this simple mechanism and it is more probable that the comparatively rapid rate of penetration of sugars is an instance of cell membrane specialization of the kind described by Davson and Reiner (1942).

In conclusion we feel we must draw attention to the significance of the results of kinetic experiments and their mathematical formulation. In our treatment of the process of penetration of sugars into the eye we have applied purely kinetic principles such as

would apply to the migration of substances across an inert membrane; the complications introduced by a possible flow of aqueous humour, as first pointed out by Kinsey and Grant (1942) and modified by Duke-Elder and Davson (1943) and Palm (1948), in no way affect the fundamental principles of the kinetic treatment provided that there is a sufficient head of pressure in the blood capillaries to make the postulated concentration differences feasible. The existence of a flow of aqueous humour through the pupil and out at the angle of the anterior chamber has been abundantly demonstrated by clinical observations, by the recent observations of Ascher on aqueous veins (1942) and by a variety of experimental procedures on laboratory animals (Friedenwald and Pierce, 1932, and Bárány and Kinsey* on the rabbit: Davson, Duke-Elder and Maurice, unpublished, on the cat): this will be made the subject of another paper but, in general, it would seem that the aqueous humour is replaced at a rate of some 1 to ·2% of its volume per minute. Such a flow could, theoretically, be maintained by a simple mechanical filtration process although the work of Bárány (1946, 1947, *a, b, c,* 1948), makes this doubtful. Moreover, evidence has been accruing from this laboratory that secretory processes are at work in the elaboration of (at any rate) certain constituents of the aqueous humour (Duke-Elder and Davson, 1948): thus the osmotic pressure of the aqueous humour is greater than that of plasma (Benham, Duke-Elder and Hodgson, 1938), as also is its content of sodium and chloride (Hodgson, 1938: Davson, 1939: Davson and Weld, 1940: Davson, Duke-Elder and Maurice, 1949).

As Bárány and Davson (1948) have emphasised, equations derived to explain the penetration of substances by a secretory mechanism (*e.g.*, that of Kinsey and Grant, 1942) have essentially the same form as those derived on a simple kinetic basis once the factor of drainage is introduced; there is thus nothing in the kinetics of the penetration of the various substances so far studied, considered as evidence by itself, that need necessarily rule out the secretory view of the mode of formation of the aqueous humour. In view of the arbitrary assumptions necessary for the formulation of equations dealing with secretory processes, arguments on purely kinetic grounds tend to be sterile, and more subtle and discriminating modes of investigation are necessary.

SUMMARY

1. In the cat and rabbit, the glucose concentrations in the aqueous humour and vitreous body are lower than would be

* Personal communication from Dr. Bárány.

expected on the basis of a simple diffusion equilibrium with the plasma. Experiments indicate that this deficit of glucose is due to the metabolism of both the lens and the retina.

2. The rates of penetration of glucose, galactose, 3-methyl glucose, xylose and sucrose into both aqueous humour and vitreous body of the cat's eye have been measured, and constants, K_A and K_V, proportional to these rates, have been calculated. No significant differences in rate of penetration into the aqueous humour were found with the first four sugars; but sucrose (a disaccharide with a larger molecule) penetrated much more slowly: polysaccharides (inulin, raffinose) cannot cross the blood-aqueous barrier in significant amounts in the normal state. The penetration rates of all sugars into the vitreous body were consistently smaller than into the anterior chamber, and an analysis of the results indicates the existence of a more selective barrier to diffusion into this part of the eye than that separating the aqueous humour from the blood. The possible physiological significance of this difference is discussed and the importance of including the vitreous body in any study of intra-ocular dynamics is stressed.

3. The rates of penetration of sugars into the aqueous humour with a constricted and a dilated pupil have been studied and it seems likely that a considerable amount of diffusion into the anterior chamber takes place from the iris. Evidence is presented which suggests that the locus of diffusion into the vitreous body is not confined to the ciliary body but occurs from all the surrounding vascularized tissues.

4. It would appear that the entry of sugars into the eye can be explained on the basis of a process of diffusion. That secretory activity is not involved in the process (so far as these substances are concerned) is suggested by (*a*) the variation of the rate of entry with the molecular size of the substances concerned, (*b*) the similarity of the rate of entry of natural sugars (*e.g.*, glucose) with synthetic sugars not found or phosphorylated in the body (3-methyl glucose), and (*c*) the evidence that sugars enter the ocular cavity from all the surrounding vascularized tissues.

5. By assuming limiting values for the area-to-volume relationship for the aqueous humour, it is possible to calculate the true permeability constants for the hexoses in the conventional units; the computation suggests that penetration is rapid in comparison with that of analogous lipoid-insoluble molecules diffusing into plant cells.

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THE STABILISATION OF THE REFRACTION AND ITS RÔLE IN THE FORMATION OF AMETROPIA*

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THE well-known doctrine of the late Swiss ophthalmologist Steiger about heredity in refractive errors (and in myopia) has not been generally accepted till to-day, although renowned authors supported it.

Vogt and his school played the leading party in this. On the other hand high scientific authorities opposed this and the dispute became sometimes very vigorous. Recently it was Lindner who was vehement in opposition to it, finding the cause of the "myopic process" once more in near work.

The question is of great practical significance. It is of vital importance to a young myopic patient whether he is allowed to read and study or not. As an example I can quote a case of a highly educated person, with stable myopia of 5 dioptres in healthy eyes. The myopia began 30 years ago in his 10th year. His parents were then strongly advised to place him in some rural occupation on account of his beginning myopia. It was only the sound common sense of the mother that averted such an unlucky turn in her boy's future.

As it is known, Steiger derived the refraction from the variation and combination of the optical elements, these being each separately inherited. An eye with a given axis results in hypermetropia, emmetropia, or myopia depending on the adjoined lower or higher refractive power. Since every component and the resulting refractive power has its own curve of variation, Steiger combined the 2 spherical ametropias together with emmetropia in one continuous line of refraction, H standing on the left, M standing on the right side of E.

Although Steiger founded the origin of myopia absolutely on heredity, and did not allow any exogenous factor, nevertheless near work played an important rôle in his theory. According to him myopia arose out of the curve of refraction adapting itself to the changed circumstances of life during a century of evolution, in the sense of Darwin's theory of selection and elimination. (Of course we have to complete it now with the newer concept of mutation.) With the growing importance of near

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work the originally eliminating factor M turned, according to Steiger, into a selective value. Myopic variations could survive and multiply. Thus myopia is an acquired feature, but it was acquired by the race and not by the individual.

Neither Steiger nor his followers took into consideration the important fact that there exists between M and the two other refractions, E and H, *in one respect a sharp contrast, that does not allow them to be placed straightaway into one biological unit:* H, and partly E, *remain mostly unchanged from early childhood,* whereas M begins later and progresses sometimes till adult age. In other words, the refraction of the hypermetropic and emmetropic eye is mostly stabilized early in life, on the other hand, the myopic eye continues to change its refraction for a long time.

Therefore the separability of M from the other refractions seemed to be unquestionable. It is easy to understand that the search for exogenous causes did not cease, and that these causes were believed to be found again and again in near work.

The formation of the refraction is undoubtedly connected with the growth of the eye. *The eyeball of the newborn has an average length of 17 mm. and a capacity of 2·2 c.cm.; that of an adult is 22·5 mm. and 6·5 c.cm.* It sounds strange, but we know almost nothing about the course and details of this enormous increase. Seefelder, an expert on the development of the eye, says our knowledge about the extra-uterine growth of the eye is very deficient and needs urgent completion.

About the refraction itself we know only that the newborn has an average H of 2·4 dioptres; this decreases to 1·8 D. till the third, and to 1·5 D. till the sixth year of life (Hartman, Herrnheiser, Steiger).

In the sixth year the axis of the eye has already reached the adult average. If the refractive power remained unchanged during *this time, there ought to have been an average* M of 14·1 dioptres.

It was Best, Wibout, Berg and others who occupied themselves with the correlations preventing this disarrangement. It was found, as it can be foreseen, that there is a positive correlation between refractive power and axis and a negative one between corneal and lenticular focal distances, but nothing was said about the substance of it.

Although it is difficult to find an explanation for a graduated correlation, it has evidently much to do with the growing of the eye. In order to maintain the right proportion between axis and *focal distance during the lengthening of the axis, the refractive* power has to decrease. The increase of every spherical surface is necessarily connected with an increase of the radius and therefore

with a lessening of the refractive power. The main rôle in this process must be played by the lens; its refractive power has to decrease greatly, at least 13-14 dioptres.

Any discordance in the correlation during the formation of the eye must lead to ametropia. Thus the definitive refraction must depend also on the time when growth finished, depending, of course, upon the starting values.

About the decrease of the refractive power as a consequence of growth we are not well informed, yet it seems to be finished in the 5th-6th year of life. There are two components, cornea and lens.

A decrease of the refractive power of the cornea is, as far as I know, not observed; on the contrary, if there is a noticeable change, it is an increase in the optical zone. Hence it is the lens that carries the burden of compensation. Unfortunately, the refractive power of the lens is not measurable by clinical methods. We know only that there is a gradual slowing down of production of lens fibres, compensated by a progressive sclerosis, and both are continuous during life. We have no means of expressing this process in numbers.

About the axis of the eye we are not much better informed. We know that its length varies between 20-30 mm.; it reaches even 32-34 mm. in extreme cases. In the majority of cases its growth ceases at the end of the 5th year, but in a considerable number it grows further, in some cases till the 23rd-24th year of life.

This is not very much, yet enough to supplement Steiger's doctrine about stabilisation, and to explain the formation of the refraction as follows: The two optical factors, refractive power and axis, are changing as long as their anatomical substrata are in growing. As soon as both factors come to a standstill, the refraction is stabilised. Thus the final refraction of the eye is determined:

(1) By the combination of the inherited optical elements.

(2) By the process of stabilisation, also inherited but independently of the optical elements.

(3) By the correlation, this being in actual fact nothing else than the relation between the two first factors.

From the standpoint of stabilisation one can attribute to every eye a "biological value" that is independent of its refraction. On this basis all eyes may be classified into three groups:

(1) Eyes of reduced biological value; the stabilisation takes place before the complete perfection of the refraction.

(2) Eyes of full biological value; the stabilisation occurs together with the harmonic perfection of the eye.

(3) Eyes of surpassed biological value; the stabilisation is late, the eye is overgrowing its harmonic measures.

I might lay stress upon the important fact that theoretically every refraction is possible in every group. A hypermetropic or myopic eye is of full biological value if it is in every respect normally developed, and its ametropia is only caused by the chance combination of the optical elements. On the other hand, an emmetropic eye may be of reduced or surpassed biological value if the E is the consequence of stabilisation at a wrong time. Supposing, for example, the combination should have resulted in a H of 6 dioptres, yet stabilisation of the axis was late, the axis became therefore 2 mm. longer. The result is E, though the eye is of surpassed biological value and in its structure myopic.

Between the biological value and the time of the stabilisation there seems to be the following connection:

(1) Eyes stabilised at the end of the second year of life are of reduced biological value.

(2) Eyes stabilised at the end of the first decade are of normal biological value.

(3) Eyes that are stabilising in the 'teens are of surpassed biological value; their stabilisation may sometimes reach as far as the third decade.

The passages being continuous, the set limits are arbitrary, but they correspond well enough with the average clinical observation.

The refraction of the new-born being hypermetropic, the eyes of the first group remain in the majority hypermetropic, and those of the second, emmetropic. The clinical manifestation of the third group is necessarily myopia; it is thus easy to understand that myopia can generally appear only in the second decade, and has a progressive character—this meaning, in our view, retarded stabilisation.

The correctness of our statements could be proved only by ample material for observation, such as, for example, the observation of 1,000 eyes, each followed individually from birth till adult age, with a continuous record of the clinically measurable data: corneal and total refraction, corneal diameter, and axis. Unfortunately, there is no possibility of measuring the lens and axis. All the many mass-examinations we have at our disposal at present are only fixed cross-sections of a population. They can be treated from various statistical points of view, but they give a very uncertain insight into the happenings and changes of the individual eye.

It would be most important to find an increasing and decreasing H as well as decreasing M. It is only increasing M

that we are, to a certain degree, acquainted with. Blegvad published a remarkable paper about 64 cases of myopia observed during a long progressive period. I published some smaller material, comprising 15 cases. In both statistics there are cases when the M was *stationary from early childhood: they could* be explained as eyes of normal biological value, showing M of combination.

There is one definite conclusion we can draw from these tables: the majority of these eyes stabilised in the second decade.

About decreasing H we know almost nothing, though its existence is very probable. There are the cases of convergent squint which "cease" later. Such cases can be explained only by a decreasing H, when a facultative H turns into a relative one in time, that is, still at a young age, when the convergence is not yet static but dynamic. We would say that, in our view, these cases are hypermetropic refractions of slightly prolonged *stabilisation. And rarely do we find in these cases E. and* exceptionally even low degrees of M.

But this is only deduction and not observation. I was, and I am, continually searching after decreasing H, but up to the present time I have not found any case where I could have stated with certainty that a decrease of the refraction had occurred. Of course, this rarity can be explained by the probable assumption that hypermetropic eyes are generally very nearly stabilised in the first years of life.

Of the greatest significance, from our point of view, is the increasing H and the decreasing M (naturally with the exception of senility and disease). Such cases must be extremely rare, as we suppose that in such cases, contrary to the general rule, the axis is already fixed while the refractive power is still diminishing. Only chance could produce such a case, or very extensive mass-observations extending over many years. It was Doppel who mentioned, in the Medical Society of Vienna in 1942, eighteen cases of increasing H found in the squint-material of Lindner's clinic. His explanation was that atropine does not produce full paralysis of accommodation in children always. Lindner, who took part in the discussion, suggested a change in the refractive power.

The two deviations of the refractive curve of the adult age, the excess and the asymmetry, have been often quoted against the hereditary interpretation of myopia. By adding stabilisation to Steiger's doctrine, they seem to be explicable without giving up the hereditary basis.

It is known that the refractive curve of the new-born is a regular binomial curve, whereas that of the adult shows an

accumulation at E and a lengthening of the myopic side (Fig. 1).

Although we are fár from being exactly informed about the details of stabilisation, we may assume that after birth all eyes are still growing (except the rare cases of microphthalmos). In the first 6 years about 60 per cent. are stabilised, in the following 4 years an additional 20 per cent., and the rest up to the 24th year (Fig. 2). The curve of stabilisation shows a turning point around the 6th year, with a maximum of the second differential quotient.

If we try to draw another curve, that is, showing the percentage of eyes attaining E in the marked year (of course, again only by rough estimation), we obtain a very asymmetric curve that shows a very marked maximum again around the 6th year (Fig. 3).

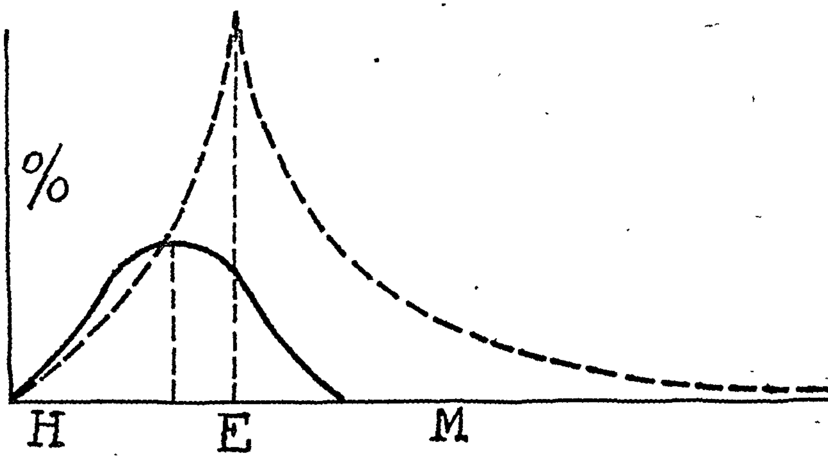

FIG. 1.

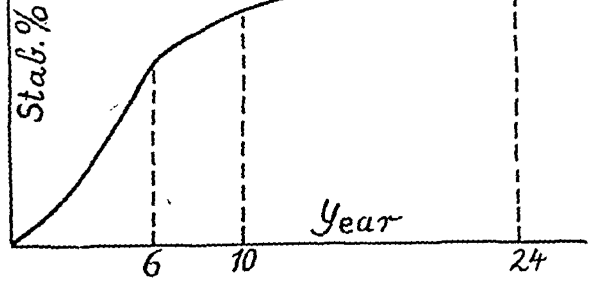

FIG. 2.

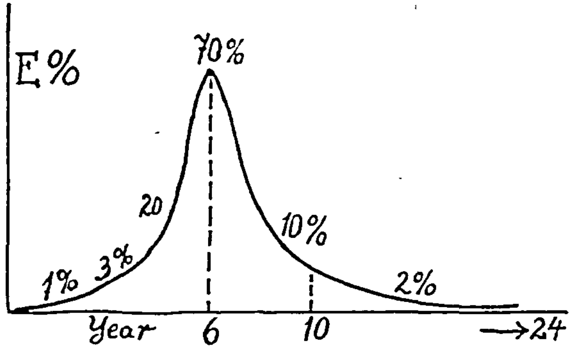

FIG. 3.

Collating the two curves, we see that the maximum of emmetropised cases coincides with the maximum of stabilised cases around the 6th year of life. Out of this summation an excess of emmetropia must necessarily arise. In other words, most eyes are wandering in the first decade of life from H through E towards M, but are in the majority of the cases stopped at emmetropia by the stabilisation.

From the curves the explanation of the asymmetry is apparent. At a rough guess we have to put the eyes of retarded stabilisation at 20 per cent. These are wandering from the left side of the binomial curve of the new-born gradually to the myopic side, and further, the later the stabilisation is taking place. On the left side there is a decrease, on the right side a corresponding increase, both in thickness and length.

The stabilisation being inherited too, in this interpretation the excess and asymmetry are a constituent part of the refractive curve, and typical for a given population.

The problem of stabilisation is closely connected with the general problems of growth. We know the organs and tissues of the body are subjected to very different rules of growth. For example, the central nervous system is far ahead of muscles and bones. The inner ear is already fully developed at birth.

Organs composed of various tissues must have their own particular rules of growing. The eye has, on the one hand, tissues of ectodermic origin, with rapid growth and quick development; on the other hand, tissues of mesodermic origin, with generally a very long period of growth. In the reciprocal influence they exert on each other the secret of the correlation is hidden. Primary importance must be given to the two interdependent but heterogeneous tissues, the retina and the sclera—a problem that has been already reviewed by Vogt.

Another closely related problem is that of the "extreme variant." Recent writers on the question of myopia—Tron, Scherer, Kronfeld and Devney—even if they are inclined to accept its hereditary origin, nevertheless make an exception of M of high degree, looking upon it as a common pathological process of exogenous origin. Yet extreme variants always display symptoms of morbid character. It is true a high degree of ametropia—neither M nor H—cannot be interpreted as a variant of combination, as such an eye, rightly stabilised, must be of full biological value and hence of normal function. But there seems to be no obstacle to explaining it as an extreme variant of stabilisation. Then we have as an extreme limit on the left side microphthalmos (theoretically even anophthalmos), and on the right side the highest degrees of M, both extremes showing various symptoms of degenerative and pathological character.

It is more than 10 years that I have been trying to find some practical consequences of the "doctrine of stabilisation," and to follow the fate of myopic patients from this point of view.

The parents of a child with beginning myopia are primarily interested in the prognosis. And really this is perhaps the most important practical question. To give an answer I try first to get some information upon the stabilisation of the parents and the antecedents. Then the construction of the eye itself gives some indication. Low corneal refraction (38-40 dioptres) is worse than higher values. A myopic (or even emmetropic) refraction of a child with a low corneal refraction may be already the sign of undue length of the axis, thus of a retarded stabilisation. The similar significance of the myopic conus and of the myopic fundus has been well known for a long time.

The recording of the yearly changes also gives indications. Although there are cases with periodic changes of increase and stability, the general rule is continually decreasing progression till the 20th year, and so we are able to foretell the definitive refraction approximately. Thus one commonly finds sufficient indications to judge whether the eye is already stabilised or nearly so, or is going to be an extreme variant.

In my opinion, with this judgment, and the reassurance of parents (and, of course, prescribing spectacles), the duty of the eye surgeon is fully completed; and should the case ever become an extreme variant, for the present we cannot do any more. The inherited duration of the stabilisation cannot be stopped by any means, least of all by restriction of near work. It is true the question of the origin of refraction and of the causes of myopia are far from being cleared up. Steiger's doctrine, as well as my

statements on stabilisation, are, in their uncertainty and unproved state, very open to attack. But still more so is the case with the opposite doctrine of the "school myopia." It is not only unproved, but one can bring weighty facts against it; as an example I refer to research on twins. There is, therefore, much to be said for the view that consequences of practical importance should not follow the doctrine of the school myopia, and restrictions in the near work of the young myopic patient should not be made.

Summary

Steiger's doctrine of the origin of refraction is enlarged with the conception of stabilisation.

Stabilisation is the cessation of the growing of the eye; its term varies with individuals. It plays a rôle equal to the combination and variation of the optical elements in the formation of the definitive refraction, and it is equally an inherited quality. The cause of the higher degrees of myopia is interpreted as retarded stabilisation.

The two weak points of Steiger's doctrine, the excess and the asymmetry of the variation-curve, are explained by the biological peculiarities of stabilisation.

A detailed knowledge of stabilisation will enable us to foretell the future of an early myopia.

Near work has nothing to do with the development of individual myopia, therefore restrictions in reading and studying by the young myopic patient should be put aside.

PIGMENT-ANOMALOSCOPY: A NEW PROCEDURE FOR TESTING THE COLOUR-SENSE*

BY

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As is known there has been up to now one method that enabled us not only to test but to measure the colour-sense in some degree: the mixing of spectral lights, as realised practically in Nagel's anomaloscope. Theory and knowledge of colour-sense and colour-blindness have been exclusively based on results obtained in this way.

The colours we see and discriminate throughout life differ from spectral lights; in opposition to the latter we call these "pigment-colours."

The important physical difference between the two forms is

* Received for publication November, 1947

well known: the spectral-colour has one wave-length or is built up at most of a very short section of the spectrum. The pigment-colour on the other hand includes all wave-lengths of the half of the colour-circle, thus being sometimes more than the half of the spectrum (*W. Ostwald's* doctrine of the "*colour-half*").

It is less well known that the physical difference becomes sometimes manifest in the sensual perception also. These are, for example, the rules of colour-mixing, with considerable divergence between spectral and pigment colours. From our standpoint there is the important fact that persons with defective colour-vision react differently sometimes, depending on whether the colours are spectral lights or pigments (Nagel, Rosmanit, Köllner). In practice it is not a rare occurrence that a deuteranomalous person makes mistakes with Nagel's anomaloscope and not with the pseudoisochromatic tables; or that a protanomalous sets a normal or almost normal Rayleigh-equation, and shows on the other hand great irresolution in the pigment-tests. It was because of this that some authors would have banished the anomaloscope from the current testing methods of colour-vision as misleading.

The question is far from being cleared up. To get some insight into the problem, the first task would be to construct an instrument by which we would be able to mix measured pigment-colours as we do with Nagel's anomaloscope.

The production of such an instrument is possible since W. Ostwald has succeeded in building up his colour-body, representing in it all pigment-colours well defined and exactly measurable. Though the polemics about the scientific value of the colour-body have not been settled definitely, its great practical value is beyond question. To the ophthalmologist who tests colour vision it is a help, and in the future it will probably enable us to penetrate more deeply into some of the unsolved questions of the colour-sense.

We have only to produce an instrument that mixes defined and measured pigment-colours additively and allows these two mixtures to be compared simultaneously, as is done in Nagel's anomaloscope with spectral colours.

The rotating disc, this well-known expedient of additive mixing, is not applicable for our purposes. Instead, we have to take cylinders which, rotating around their axes, mix the colours of their surfaces as well as the disc. This has been done. We took two parallel cylinders side by side, that could be pushed independently of each other to and fro during rotation. There were some technical details to solve, but we had at last the necessary construction, the "pigment-anomaloscope," fully coming up to our expectations. It proved shortly to be a useful and readily applicable instrument for testing and studying colour-vision.

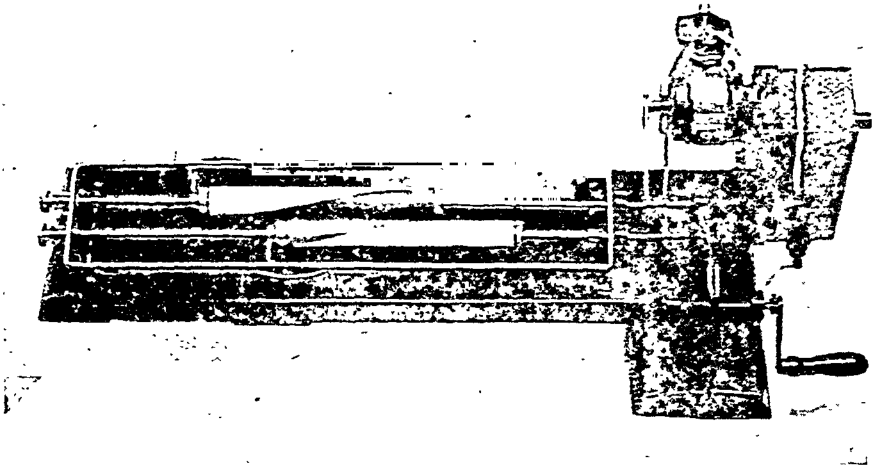

FIG. 1.

The pigment-anomaloscope uncovered.

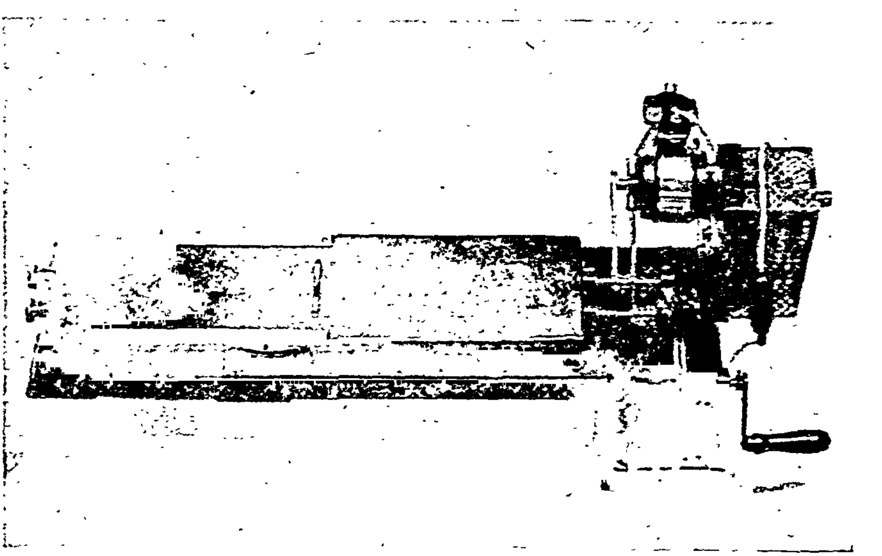

FIG. 2.

Pigment-anomaloscope covered, showing the observation slit.

The model we have been using is reproduced in Figs. 1 and 2. It is a simple artisan-made piece, but shows all the important features. It works alternately either by hand or by electricity. The two cylinders glide on steel axes and are changeable. On their surfaces are the colours to be mixed, on detachable papers. These are, of course, carefully selected and determined according to Ostwald's colour-body. For example, there are "*8 na*" red and "*20 na*" green on the one cylinder

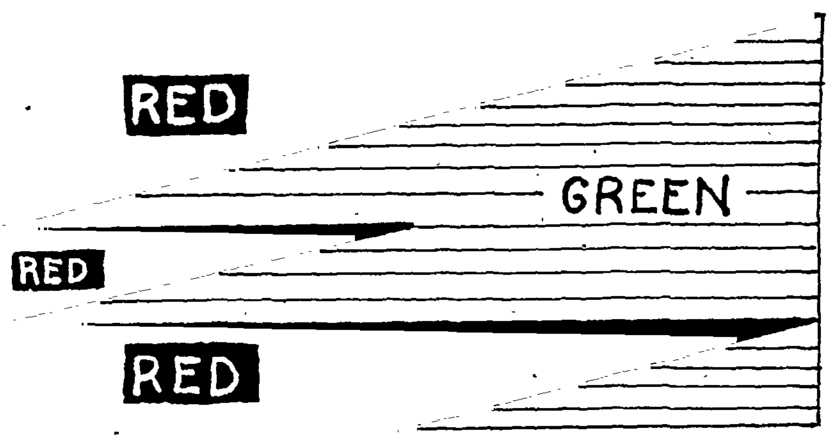

FIG. 3.

The surface of the cylinder with the two colours to be mixed, showing simultaneously the middle.

and "*a*" white and "*p*" black on the other, this being the basic pigment-mixture of red-green, matched with neutral grey.

The surface of the cylinder is a parallelogram, it is diagonally divided for the two colours. In order to get a more perfect mixture the surface can be sub-divided into narrower parallelograms (Fig. 3).

We see on the left end of the lower rotating cylinder pure red, on the right end pure green. Towards the middle both colours are getting more and more greyish, till in the middle they meet in a small stripe of neutral grey. On the upper cylinder there is a continuous change of grey from black to white. Both cylinders are covered with a black metal plate with a linear slit in it (Fig. 2). The examinee sees only as much of the cylinders as appears in this stenopæic opening.

Both rotating cylinders can be pushed to right and left by handles. Simultaneously with the two handles there are two indicators moving on tape-measures, showing the position of each cylinder. The zero indicates that the middle of the cylinders are in the slit.

When the apparatus is in gear, the examinee has nothing else to do but to push both cylinders to right and left till he sees in the slit above as well as below the same colour, neutral grey. In this position the indicator of the lower cylinder shows the amount of red and green necessary to obtain the match. In a normal trichromatic case this is fifty-fifty, the indicator should point to zero, or be very near to it. That adjustment corresponds fully with the normal Rayleigh equation.

The protanomalous requires more red, the deuteranomalous more green. In matching, the indicator stands somewhere on the right or left side of the tape-measure, showing the necessary amount of the colours. To make a record we have only to note the side of the tape-measure (f.i. D or P), and the figure at which the indicator points. For example, "*D 34*" indicates that the examinee found equality on the green side of the cylinder, 34 mm. from the centre, hence took 67 per cent. green and 33 per cent. red instead of 50-50 of the normal.

To register the grey cylinder is commonly superfluous, as it has only a theoretical value. We use it in practice only to give the examinee a grey to be matched.

There is a parallel between the recording of our instrument and Nagel's anomaloscope. The zero of the latter (that is the equation of the normal) is usually between 50 and 60 (mostly at 54). Higher figures denote protanomaly, lower ones deuteranomaly. We could as well put zero in the place of 54, in which case the records of both anomaloscopes might obtain the same meaning (except the fundamental difference). On that account Nagel's anomaloscope is well replaced by our instrument.

But it is more than a simple supplement, as it completes Nagel's anomaloscope in many respects. These are some of them:

(1) The cylinders being changeable, all imaginable mixtures are easily effected. Out of these the yellow-blue mixture has a practical value in two directions: it is a test for exposing simulation, and we might find by its help the rare condition of tritanomaly.

(2) Comparing the results obtained on both anomaloscopes, we are able to get some insight into the question of the difference between the perception of the same colour whether of the spectral or of pigment variety. The direct comparison of the results has been made possible by the well-known quotient of v. Kries (Q), deducted from the relation

$$Q = \frac{\text{green}}{\text{red}}\,(\text{normal}) : \frac{\text{green}}{\text{red}}\,(\text{examinee}),$$

green and red meaning the amount of colours in per cent. used to obtain neutral grey.

The examinee being normal, the Q has to be necessarily 1. In the very same manner the Q of a protanope has to be more, of a deuteranope less than 1. The great value of the *quotient* consists in eliminating all differences that arise out of the differently constructed and adjusted types of anomaloscopes. Thus the quotient gives a generally valid character of a person's red-green perception. If there were a discordance between the spectral and pigment quotient of the same person, an explanation could be found only in a difference between the perception of the spectral light and pigment colour. We found such cases sometimes in our investigations. There is, for example, the analysis of the following case:

On Nagel's anomaloscope a deuteranomalous examinee sets the equation at 30. The drum of our anomaloscope is divided into 88 lines. The normal equation is at 54, hence the first fraction of v. Kries' quotient is 34/54. The fraction of the examinee being 58/30, *the spectral quotient is found to be 0·32*.

The cylinder of the pigment-anomaloscope has a length of 200 mm. and a circumference of 100 mm. The zero being in the middle, the normal equation is 50/50. At 100 mm. it is from 50 to 100 per cent. of colour, we obtain the numerator of the division by adding to 50 half the number set by the examinee. The number completing this sum to 100 is the denominator.

The same deuteranomalous patient found neutral grey on the pigment-anomaloscope at D 32, hence the division of the quotient is 66/34. The quotient itself is 0·51.

We see there is a difference of 0·19 between the spectral and the pigment quotient. We may conclude that the perception of green has been 19 per cent. better when presented in pigment form. The examinee passed the pseudo-isochromatic tests faultlessly. *This fact seems to confirm our conclusion.*

(3) The pigment-anomaloscope is well applied to determine the threshold of the colour-stimulus—a new possibility. In practice there did not exist such a method. It has not only theoretical interest but it makes a welcome completion of the colour-sense tests.

We have only to put the colour on to the cylinder in the shape of a triangle, the two supplementary colours on the two ends of the cylinder, and interpolate white triangles (Fig. 4), the latter serving to eliminate the disturbing influence of the light-sense.

The examinee has to find the inner borders of the coloured impression. Starting from the middle, he sees only a change into grey in the beginning. He stops as soon as he has recognized a coloured impression. Of course, we do not obtain an absolute value, but in equal circumstances a comparable value.

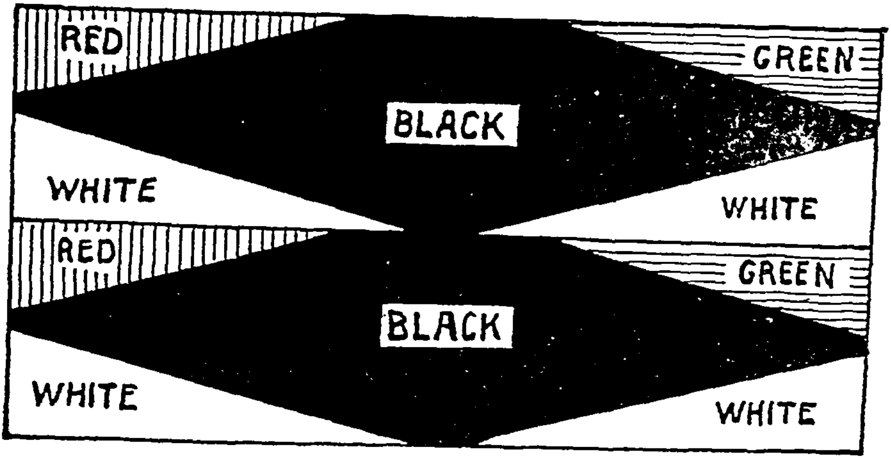

FIG 4.
Arrangement of the colours for threshold examination.

Anomalous trichromats always display such an increase of the threshold that it alone is sufficient to reveal their anomaly. We find generally an increase on both sides, yet protanomaly shows a greater increase in red, deuteranomaly in green, following the theory of Young-Helmholtz.

With the aid of threshold-investigations perhaps we shall be able to penetrate deeper into some hitherto obscure problems of the colour-sense. There is, for example, the question of Wölflin's "relative red- and relative green-sightedness," also the normal varieties type I and type II of Tschermak-Seysenegg, all probably associated with threshold differences.

There are the rare but interesting cases of colour-weakness with a normal equation (Edridge-Green). In such cases we could suppose an equally increased threshold for both complementary colours; of course, investigations in this direction are still lacking.

(4) Finally it may be mentioned that we are able to reproduce every continuous colour-band in a simple way on the pigment-anomaloscope, and also the spectrum. Naturally they are composed only of "colour-halves," nevertheless they show every peculiarity of the original in the sensual perception and are therefore applicable.

Conclusion

I have tried to show that the pigment-anomaloscope would make a useful completion of colour-testing. It could even enlarge our knowledge of colour-vision. The model reproduced in Figs. 1 and 2 is, of course, in many respects rough;

made by a skilful mechanic it could take the form of a faultless, silently running and exact instrument. It could even be further improved for scientific purposes. It would be necessary, for example, to make its illumination independent of daylight; to narrow the field of observation to points and to bring them together into one round divided surface, observed through a telescope, similar to that of Nagel's anomaloscope. For the present I had to content myself with the model at hand.

A NEW METHOD OF APPLYING THE SCREEN TEST FOR INTER-OCULAR MUSCLE BALANCE

BY

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THE apparatus described in this communication was developed at the Manchester Royal Eye Hospital as the result of a series of experiments designed to overcome certain difficulties experienced in the application of the Hess screen test.

In the Hess method, a colour separation system is used to obtain dissociation of binocular vision, and the difficulties experienced were all attributed to this. Such a system, whilst theoretically capable of perfect results, is apt to be inefficient in practice, because of the difficulty of manufacturing materials of the exact and stable colours required for the screen, pointer, and goggles. Even if initially correct, these are likely to deteriorate with age and use. If the colours of the components used are not exactly correct, the dissociation obtained is only of relative degree, and errors then are liable to occur in the test. Thus the red pattern of the screen may be faintly visible through the green glass, or the green pointer through the red glass. The resultant accuracy of the test depends on the brightness of these images compared to the correct ones.

If the secondary image allows of uniocular localization of the pointer to the cardinal points through either glass, the test is rendered useless; or even if the position of the green pointer is seen through the green glass, and related, as it should be, to the apparent position of the red cardinal points seen through the red glass, still the result may be inaccurate, owing to the fusional stimulus caused by the screen pattern being visible, to a greater

or lesser degree, to each eye, for this distorts the possible angle of deviation.

Even when colour separation is perfect, errors may still occur, for a keen observer may be able to effect monocular localization of the pointer to the cardinal points if he notices the eclipse of the red screen-pattern which takes place as the pointer is moved over its surface.

Many patients have trouble with the test for yet another reason, as they fail to recognize the pattern of the screen, or the position of the pointer, because of the low level of contrast present, when these are seen against the black background of the screen through red-green goggles. As a result, they cannot appreciate what is required of them to complete the test. This inability is partly due in a small proportion of cases to some defect of red-green vision in the patient under test.

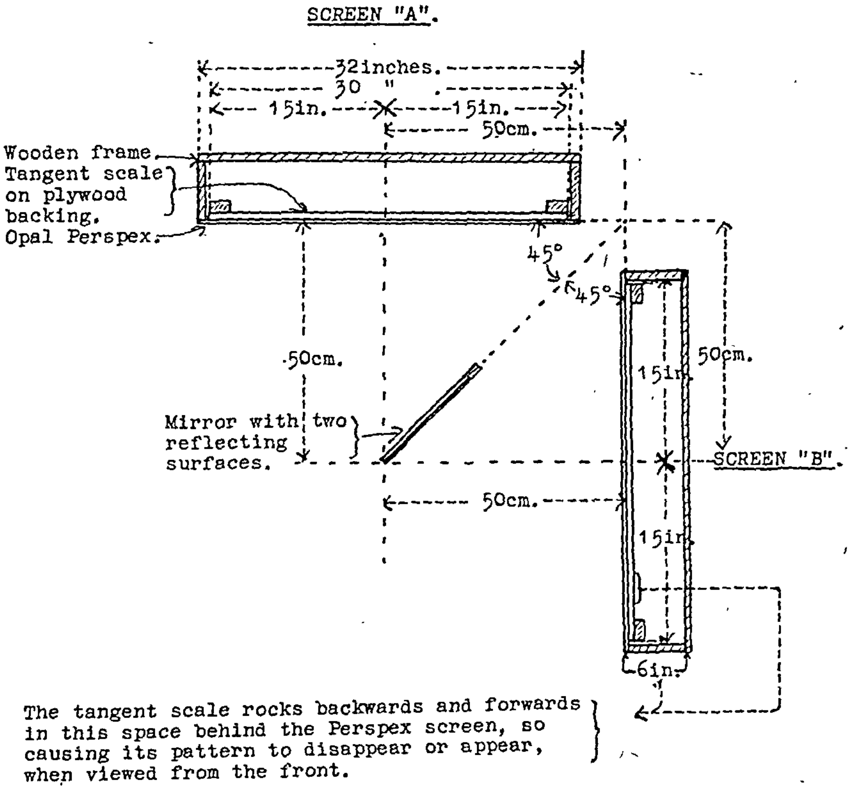
In order to obviate the possibility of such errors and difficulties, and to make the screen test more easy to perform, it was re-designed around a more efficient and stable method of dissociation. The tangent scale pattern used on the Hess screen was retained, but as colour separation was not used, the scale was printed in black on a white background to ensure clarity. The Hess test recording charts are used as previously, and the graphs produced are interpreted in exactly the same manner as before.

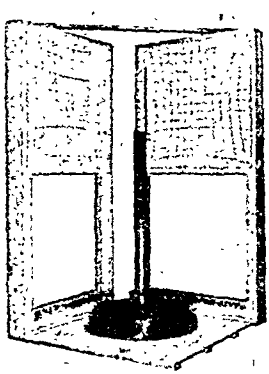
The principle of this new development of the screen test is that dissociation is obtained by a plane mirror placed before one eye. The mirror has a reflecting surface on each side, and is placed in such a position between two identically printed tangent scales erected at right-angles to each other, that a symmetrical system is formed, in which each scale is situated at the position to which the virtual image of the other scale is projected, when seen in one or the other surface of the mirror. Thus the patient sees different but identical scales exactly superimposed. To avoid fusional stimulus and afford a blank surface before the plotting eye, each scale is so constructed that its pattern may be made to appear or disappear as required during the test.

Reference to the illustrations will amplify the following description of the construction and use of the apparatus.

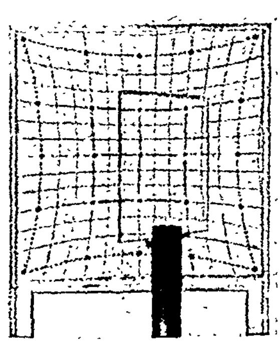
Two tangent screens are used, each being a composite assembly of a plotting screen and tangent scale. Each plotting screen consists of a sheet of light opal perspex, 32 in. square x $\frac{1}{8}$ in., mounted on the top half of a wooden stand, 64 in. in height. Behind each screen is a tangent scale, 30 in. square, the pattern of which is exactly as is used on the Hess screen, that is, one having a working distance of 50 cm. It is, however, marked in black lines on a white background. The tangent scale is sup-

PLAN OF MIRROR SCREEN TEST

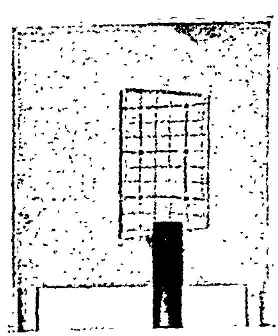




General view of apparatus. Screen "A" on the left. Screen "B" on the right.



Screen "A" with virtual image of screen "B" seen superimposed in the mirror.



Screen "A" with tangent pattern suppressed ready for plotting projection of left eye. The right eye fixing the mirror image.

(Photographs by courtesy of the Department of Medical Photography, Manchester Royal Infirmary)

ported by a plywood back-board held on two wooden struts, which hinge on to the bottom of the frame holding the plotting screen. The tangent scale is thereby enabled to rock backwards and forwards behind the plotting screen, so as to be either in contact with it, when its pattern shows clearly through the opal perspex, or separated from it by a distance of about 4 in., when its pattern is so diffused as to be invisible.

The two tangent screen assemblies are secured in relation to each other on a firm baseboard, being also braced by a top strut. Their position is such that the two plotting screens are vertical and at right-angles to one another, and so that with both tangent patterns made visible, the centre horizontal lines of the scales are each at the same height from the base, and the centre vertical lines each parallel to, and 50 cm. distant from, the plane of the other screen. These adjustments must be accurately carried out, as upon them and the position of the mirror, rest the exact alignment required for the success of the test.

The mirror is made from two $\frac{1}{8}$ in. thick sheets of plate-glass, each 12 in. square, silvered on the rear surface and cemented together back to back so as to give a reflecting surface on each side. This mirror is mounted on a rigid steel stand equipped with screwed bolts in the base, whereby the position of the mirror can be adjusted.

The mirror on its stand is placed in position between the plotting screens, so that its reflecting surfaces lie in the plane which bisects the angle between them—that is, at angle of 45 degrees to either screen. The front edge of the mirror must be on a line 50 cm. distant on perpendiculars drawn from the centre verticals of either tangent screen. The height of the mirror should be such that the line bisecting it horizontally is level with the centre horizontals of the tangent screens.

The accuracy of the alignments carried out may now be checked by viewing each screen, and the part of the other screen as seen in the mirror, from a distance of about 6 ft., when the lines of the virtual image should be continuous with those of the screen on which it is superimposed. If this is found to be correct the apparatus may be considered ready for use.

Two pointers are used in the test, each consisting of a metal rod about 50 cm. long. The one used by the patient has a ring at its tip after the style of the Law pointer often used in the Hess test. The one used by the operator has a small disc at its tip half the diameter of the ring on the other.

The patient sits close to the mirror, with his nose touching its front edge. He faces screen "A" if the projection of his left eye is to be tested, or screen "B" if his right is to be tested.

The charts obtained by plotting from these positions correspond to those obtained by the Hess method when wearing the green glass before the left and right eyes respectively.

Suppose the patient to be facing screen "A." His right vision is intercepted by the mirror, in which he sees screen "B" projected forwards as a virtual image, to appear as if superimposed upon screen "A." The patient's left eye, its vision unobstructed by the mirror, sees screen "A" directly, but cannot see screen "B" as this is situated laterally. Nor can the right eye see screen "A" because of the mirror. Binocular vision is, therefore, completely dissociated, but similar tangent scales are exactly superimposed by the symmetry of the apparatus.

The tangent pattern of screen "A" is now suppressed, leaving a blank surface before the patient's left eye. The tangent pattern of screen "B" still remains visible to the patient's right eye, appearing as a virtual image projected on to the blank surface of "A." The operator now indicates on screen "B" the cardinal points which he desires the patient to fix, by holding the disc at the tip of his pointer over each position in turn. Small oscillatory movements are made with the disc over the cardinal point, so as to stimulate more exact foveal fixation by the patient, who observes the virtual image of the disc through the mirror. These movements also help to eliminate alternating macular suppression, which sometimes causes trouble during the test. The patient holds the ring-tipped pointer in his left hand and with it encircles the apparent position of the disc. As the ring is seen only by his left eye against the blank screen "A," it indicates the foveal projection by this eye of the image of the disc seen by his right eye, depending upon the cerebral relation of the two foveal pathways, and the interocular muscle balance. The position of the ring is now measured by momentarily causing the re-appearance of the tangent pattern on screen "A."

The cardinal points required to complete the square pattern covering the ocular muscle actions are now plotted in sequence. The measurements taken are entered on the left-hand side of the diagnosis chart, exactly as plotted by the patient on screen "A."

It will be realized that the patient sees the virtual tangent scale reversed by the mirror in the horizontal meridian, but as the nine cardinal points are symmetrically situated about the centre line, the phenomenon of image reversal need not be taken into account when all nine points are plotted in sequence. Only if a single point is under consideration during plotting need this reversal effect be remembered.

To test the right projection, the patient must change his position so as to face screen "B." This time he fixes the cardinal

points indicated on screen "A" with his left eye, which now confronts the other reflecting surface of the mirror. The projections of the visual axis of the right eye corresponding to the various points fixed by the left, are now indicated by the patient, who this time holds his pointer in his right hand and guides it by the vision of his right eye over screen "B." During this half of the test the tangent pattern of screen "B" is suppressed during plotting.

The measurements taken are transferred to the right-hand side of the diagnosis chart, which on completion is interpreted in exactly the same manner as is a record of the test done by the red-green dissociation technique of Hess.

The method of construction described above is not the only one applicable to the screen test by mirror dissociation, but was one adopted for the sake of convenience and according to the workshop facilities at our disposal.

Possibly a better method of superimposing the tangent patterns on to the plotting screen is a rear-projection system, in which the image of a tangent scale printed on a transparent base, is thrown on to an opal screen by back-lighting. By this means control of the pattern is obtained through an electric switch. Messrs. Theodore Hamblin, Ltd., of Wigmore Street, London, are conducting experiments on this system with a view to production of the apparatus.

Another way is to employ symmetrically mounted cork or suchlike screens, on which the plotting of the patient's projection is mapped by pins. The cardinal points for fixation are shown by a transparent tangent scale, which, on removal to the mirror image position, is also used to measure the position of the plotting pins.

Other variations, such as an automatic recording system, by which the projection is transferred directly to the graph-paper, are possibilities which have not yet been tried.

Whichever method is adopted, it will be realized that, as the apparatus requires to be installed as a semi-permanent fixture, and as its manufacture is more exacting, the initial cost will far exceed that for the original Hess screen test. The advantages offered in rapid, accurate and trouble-free results far outweigh the initial difficulties and expense involved.

The apparatus has been in daily use at the hospital at Manchester for almost a year, and during this time many hundreds of patients have been tested upon it. Although many of these had previously failed to perform the Hess test, not one failed to perform the mirror dissociation method. Amongst the numbers tested were several small children, all of whom readily gave readings which could be interpreted with confidence in their accuracy.

THE OPENING OF THE INSTITUTE OF OPHTHALMOLOGY, LONDON

ON November 4th an event occurred which it is hoped will be of some significance in the development of British Ophthalmology — the formal opening of the Institute of Ophthalmology, a unit of the British Post-graduate Federation of the University of London.

London, of course, has been a centre of ophthalmological teaching for many years — indeed, since the founding of the School at Moorfields in 1810. For over a century it remained the principal focus of ophthalmological inspiration for the English-speaking world. As research grew more complicated, however, and demanded for its satisfaction not merely the routine of the clinic and the simple facilities of a pathological laboratory where the ophthalmoscope and the microscope were sufficient equipment, but, in addition, a host of specialists — physical, physiological, biochemical and immunological — each with his elaborate equipment and all working as a team, it became apparent that if London were to maintain its position as a centre of advancement and progress, a more co-ordinated and systematized organisation was necessary.

Some twenty years ago a move was made, largely under the inspiration of Sir John Parsons, to remedy this defect, but financial support was not forthcoming and loyalties and traditions acted as a break to radical changes. At the same time, in the years before the second World War, the development of the British Post-graduate Medical School was a harbinger of future events and it maintained a close interest with the Medical School at Moorfields.

After the war, the British Post-graduate Medical Federation was formed within the University of London and the Medical School at Moorfields was invited to join the Federation as an Institute of Ophthalmology. With a view to co-ordinating all that was best in London, Moorfields, the Central London Ophthalmic Hospital and, later, the Royal Westminster Ophthalmic Hospital, became amalgamated by an Act of Parliament. Such a combination gave scope for wide planning within the three units and it was decided that the building of the Central London Ophthalmic Hospital should be converted — not a very extensive reconstruction — into a research and teaching Institute, and that the other two hospitals should act as associated clinical units. The result, it is true, is not entirely satisfactory, for the partial divorce of lecture rooms, library, museum, routine and research laboratories from the clinical departments, is a considerable handicap. It is a handicap, however, that it is hoped to overcome as soon as the economic conditions of the country allow new medical buildings to be constructed on a large scale. In the meantime, in the spring of 1947 the practice of the Central London

Ophthalmic Hospital began to be transferred, reconstruction work was pushed ahead and by November 4th, 1948 sufficient of the building was ready to allow a formal inauguration ceremony to be held.

The new Institute comprises a building of six floors of which the basement is given over to a cafeteria, kitchen, students' sitting rooms and cloakrooms, technicians' rooms, workshops and store-rooms. On the ground floor are the administrative offices and a department for clinical teaching and research clinics. A small orthoptic department has been retained for research purposes. The first floor houses a large department for medical illustration, equipped and staffed for photography in all branches, including fundus photography, cinematography and fundus drawing, and also contains a suite of rooms for the more elaborate types of clinical research. On the floor above are the library and museum, built up from the material available from the three parent hospitals, offices for the British Journal of Ophthalmology and Ophthalmic Literature, and a lecture hall to hold 100. Laboratories for morbid histology, bacteriology and allergy occupy the major part of the third floor. The remainder of the building is occupied by twenty-three laboratories fitted up for research in physiological optics, physiology, electro-physiology, biochemistry and radiography, with appropriate technicians' rooms, operating theatre, five animal rooms and appropriate accessories. During the present session there are 126 post-graduate students from many countries of the world, and at the time of its opening the Institute has on its staff 15 full-time research workers.

The opening ceremony was held on the afternoon of November 4th under the Chairmanship of the Earl of Rothes — Chairman of the Committee of Management of the Institute — before an audience of representatives of the University and the British Postgraduate Medical Federation, the provincial and Scottish Universities, together with many of the past and present staff of the three hospitals and the Institute. Lord Rothes briefly outlined the history of the development of the Institute and suitably welcomed the three guest speakers Sir John Parsons. Professor Alan Woods and Professor Weve — representing British, American and European ophthalmology who also gave inaugural addresses.

Sir John Parsons spoke of the two functions of the Institute. So far as teaching was concerned, the reputation of the three associated hospitals was already high, and with the greater facilities now available, it should become still higher in the future. So far as research was concerned the Institute was indeed fortunate for it had on its staff the type of men who were able and willing to do research and it also had the support of the Medical Research Council. It was quite illusory to imagine that the procurement of a building and the provision of finance could of themselves produce

original work of value: the success of research depended on the work of men with a flair for it. At the same time, an Institute of this type should only be looked upon as the first step in the right direction: co-ordination with general medicine and surgery as well as with the fundamental physical sciences was a necessity and that means an intimacy with a general hospital and university laboratories which must be topographical as well as spiritual.

Professor Alan Woods expressed his pleasure in participating in the inaugural exercises which he thought marked a new epoch in the advance of British ophthalmology. He brought with him the good wishes of American ophthalmology and particularly the congratulations of the Johns Hopkins University School of Medicine. He spoke of the great part played by Great Britain in the development of ophthalmology, and pointed out that, while the problems of clinical diagnosis and therapy were ably dealt with in the past by the large independent or semi-independent eye hospitals of Europe and America, a new type of Institute such as the present was now necessary wherein to tackle the problems of the future. The obvious clinical problems had been dealt with; the advances of the future must be solved by the co-operation of specially trained ophthalmologists with fellow scientists in a host of other fields, ophthalmic research must be co-ordinated with modern medical investigation and must be an integral part of the life of a University carried out in fellowship with colleagues in other branches of medicine and science. In extending his good wishes for the future of the Institute, the construction of which at this time of stress and reconstruction was typical of British courage, he said that anything his own School of Medicine could do to assist would be only a small acknowledgement of the debt owed by America to British ophthalmology.

Professor Weve traced the history of the development of ophthalmology in Europe, how it started two centuries ago with the surgical renaissance in France under the inspiration of Daviel, migrated after the French Revolution to Austria, revived under the stimulus of Helmholtz and v. Graefe in Germany and Donders and Snellen in Holland, and later, particularly in its optical aspects, in Scandinavia. Throughout all this time the place of England was high. In the earlier days the genius of Newton and Young was continued in clinical ophthalmology by such men as Bowman and Mackenzie, and the torch has been carried down to our own day by such men as Parsons. The two wars which have devastated Europe have not been without their influence in this development, but it was a great day not only for British ophthalmology but for world ophthalmology, that despite the ravages of war, sufficient enterprise and courage had been at hand to start an Institute of this type.

After tea and a tour of the Institute, the Lecture Hall was filled for a delightful inaugural address by Professor Woods on "Experimental Studies on the Pathogenesis and Therapy of Ocular Tuberculosis"; this will be published in a future issue of this journal. In the evening an enjoyable dinner was held at Claridge's Hotel, at which Professors Weve and Woods proposed the toast of the Institute, and Sir Stewart Duke-Elder replied.

CORRESPONDENCE

APOLOGIA PRO VITA MEA

To the Editorial Committee of

THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—On giving up the post of senior editor I wish to thank all my colleagues on the Editorial Board for their forbearance and the great kindness shown to me for so many years. And I should also like to thank those subscribers who have from time to time written me appreciative letters. To know that I had the good will of the fraternity has been a great help. It might be thought that an editor's life comes within Mr. Mantalini's definition "one demd horrid grind," but I have not found this to be the case and my journal years have been very happy ones indeed.

Sir William Osler once wrote something to the effect that it was wonderful how a bad boy may fool his fellows if he once gets to work. I believe my only editorial assets have been two in number: first, writing has always come easily to me, and in saying this I hope that I have not been unmindful of the dictum of Edward Fitzgerald, that "easy writing often makes for difficult reading": secondly, I was early in life introduced to good English literature. In connexion with my first point I recall one of my prep. school reports in which my essays in divinity were commended, the master adding "he has a good fund of English on which to draw." Perhaps any facilities I may have shown in the concoction of annotations may be traced to this early source. With regard to my second point, the same master who praised my English essays (the less said about my efforts in Latin the better) was wont to read aloud to those of us who cared to listen, and in this way introduced me to Pickwick and The Rose and the Ring. My father also used to read out to us in the holidays and he took me through most of the Waverley Novels. Scott, Dickens and Thackeray are good foundations in English literature. And a parson's son who has to attend church twice a

Sunday, clad as Hood clothed the Devil, that is to say in his Sunday best, must be a hopeless ass if he does not learn in time to appreciate the extraordinary beauty of much of the prose of the Book of Common Prayer.

It might be thought that with my early theological leanings I should have done better to enter the Church, especially as a family living was, and is, situated among the hills of South Shropshire. But I had the gravest doubts as to my ability ever to become what one of the bidding prayers calls a discreet Minister of God's word. I felt, too, that I could never fill the pulpit from which my maternal grandfather had thundered at the rude forefathers of the hamlet who slept in the box pews beneath. The Rectory was a mile from the church, high up on the hill side, facing due east, and bitterly cold in winter.

I have never regretted that I chose the medical rather than the clerical profession. My choice of medicine was fortuitous, and was due to the Gloucester smallpox epidemic of 1896. My home was nowhere near Gloucester, but my father decided that the household should be vaccinated. As I was being done, it suddenly struck me that it didn't seem to be particularly difficult, and that here was a career in which the fool of the family might make good. My enthusiasm, however, received a couple of shocks before I left school. The first came from a schoolfellow, himself the son of a doctor, who asked me what I was to do in after life, and when I said I hoped to be a doctor, replied "do you think you have enough brains to pass the examinations"? The second shock was delivered by my housemaster, who, when I asked him if he thought I could matriculate at the University of London, said "my dear boy, it's no use, you simply haven't the brains." I must confess that on my school record they were both abundantly right, and only hope that my subsequent career has done something to correct the verdict.

When I joined the staff of the British Journal of Ophthalmology I had already had some practice in correcting proofs with E. E. Henderson. I had my consulting room in his house during the time that he was editing the Ophthalmic Review. We neither of us had much practice, and he would occasionally give me a spare set of proofs to correct, and go through them with me afterwards. I owe him a great deal, for he taught me much. Among other things, I learned to beware of the split infinitive, sentences ending with prepositions and those starting with a past participle. Tautology, journalese and slang were all anathema to him.

As soon as I joined the Journal I found I could always take my difficulties to Sir John Parsons and be sure of getting sound advice. I must have made myself a proper nuisance to him, to use an East Anglian expression; but he never seemed to mind, and I soon felt

that if he were satisfied naught else mattered. We all know how much he has done for British Ophthalmology, but only the editorial staff know fully what he has been to the Journal.

I am proud of having worked with him for the Journal, and would like to express my gratitude to him for his exceeding great goodness to me over a period of more than forty years.

In saying goodbye, I wish the Journal many years of prosperity and usefulness, and hope that those who work under the new arrangements will enjoy it as much as I have done in the past.

Yours faithfully,

R. R. JAMES.

WOODBRIDGE.

To R. R. J.

To the Editorial Committee of

THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—It is with very genuine admiration and honour mingled with sadness that I salute my Editorial Chief, Mr. Rutson James, as he passes to well-deserved retirement. Like many famous men and women in our island history he comes from a large family brought up in a country parsonage, and belongs to a generation nurtured in that age of character and grace during the reign of Queen Victoria. The stock from which he comes, the background of his childhood and his training at Winchester, where "Manners makyth man" combined to make him a perfect example of the English gentleman. His courtesy to me through more than 19 years of happy association with him on the staff of the British Journal of Ophthalmology, and indeed to everyone he has dealt with, has been constant, and his sense of duty and rightness of the highest order. At times I have felt that he has been too lenient in handling my editorial misdeeds and shortcomings on occasions when I deserved stern rebuke. True to his character he would always take the full blame, and endure the discomfort of mind that went with this, for any fault committed by a subordinate, and this, for a nature as acutely sensitive as his, is a tribute to his courage and loyalty.

In this changing world men of his calibre and integrity are becoming rarer in all walks of life, and so we appreciate and value them the more. I could not have had a better chief, a wiser counsellor to whom to appeal for advice, or a more loyal friend. I owe him an immense debt for all he has taught me from his wide experience in literary matters, for the enjoyment of his whimsical humour, and for his high example of truth and honesty in writing and in all his dealings.

Yours faithfully,

H. B. STALLARD.

81, HARLEY STREET,
W.1.

NOTES

The Ophthalmological Society of the United Kingdom. Annual Congress, 1949

THE Annual Congress of the Ophthalmological Society will be held at the Royal Society of Medicine, 1 Wimpole Street, London, W.1, on March 31, April 1 and 2, 1949.

The subject for discussion will be "Corneal Grafting," which will be opened by Dr. R. Townley Paton (New York), Professor A. Franceschetti (Geneva), Professor G. P. Sourdille (Nantes), and Mr. J. W. Tudor Thomas (Cardiff). Members who wish to take part in the subsequent discussion are advised to intimate their intention before the opening of the Congress. It is emphasized that no member may speak for more than ten minutes.

Members wishing to read papers are asked to send the titles to Mr. Bridgeman as soon as possible. Abstracts of papers, which will be circulated at the Congress and subsequently to the leading ophthalmological journals abroad, should be submitted *not later than January* 31, 1949.

The Friday afternoon will be devoted to pictorial demonstrations of subjects of special interest. Members who wish to contribute are asked to communicate with Mr. Bridgeman as soon as possible.

The Annual Dinner will be held on Thursday, March 31. It is hoped that it may be possible for members to bring guests.

On account of the difficulty in obtaining hotel accommodation in London, all members who will require it are advised to make their arrangements in good time.

Hon. Secretaries { T. KEITH LYLE. G. J. O. BRIDGEMAN.

* * * *

Royal College of Surgeons of England. Ophthalmology Lectures

THE following lectures will be delivered at the College in Lincoln's Inn Fields, London, W.C.2:—*Tuesday, March 29, 1949*, Professor A. Franceschetti (Prof. of Ophthalmology, University of Geneva), Cataract Associated with Lesions of the Skin, at 5 p.m.; Professor G. B. Bietti (Prof. of Clinical Optics, Pavia University), Protein and Amino-Acid Deficiencies in Ophthalmology, at 6.15 p.m. *Wednesday, March 30, 1949,* Professor E. Hartmann, Psychosomatic Symptoms in Ophthalmology, at 5 p.m.; Professor H. J. M. Weve (Prof. of Ophthalmology, Rijksuniversiteit) (the subject to be announced later), at 6.15 p.m.

W. F. DAVIS,

Secretary,

Postgraduate Education Committee.

THE BRITISH JOURNAL OF OPHTHALMOLOGY

FEBRUARY, 1949

COMMUNICATIONS

A FUNDUS DYSTROPHY WITH UNUSUAL FEATURES

(Late onset and dominant inheritance of a central retinal lesion showing oedema, haemorrhage and exudates developing into generalised choroidal atrophy with massive pigment proliferation)

BY

ARNOLD SORSBY *and* MARY E. JOLL MASON

LONDON COCKERMOUTH

with the assistance of

NORMAN GARDENER

WATFORD

IN AN earlier study (Sorsby, 1940) attention was drawn to the polymorphism of the dystrophies of the macula. It was shown that when such genetic affections as " family choroiditis " (Doyne, 1899, 1910), the central fundal disturbances in elastosis dystrophica (angeoid streaks—Doyne, 1889; Plange 1891; Grönblad, 1929;

Böck, 1937-38; and Prick, 1938) and central choroidal sclerosis (Sorsby, 1939) are excluded, the residual group of macular dystrophies of an atrophic character, generally associated with the names of Stargardt and Behr, cannot be regarded as a sharply defined clinical entity. Evidence was brought forward for the existence of a variety of additional types: exudative, heavy pigmentary, and "inverse retinitis pigmentosa." It appeared from the literature (Mazzi, 1934 and Waardenburg, 1936, 1938) that there was also the possibility of a haemorrhagic type but the evidence was regarded as unconvincing. It was also suggested that Doyne's choroiditis was a variant of the "exudative type," and that each of the four main forms of macular dystrophy—the atrophic, exudative, pigmentary, and inverse retinitis pigmentosa types—showed subsidiary variants in different families. As to the age of onset of these affections, it was shown that Behr's classification of lesions as occurring at birth, early in childhood, adolescence, early adult life, and at the beginning of involution, and possibly also at old age, was distinctly schematic; there was nothing to support his suggestion that the lesions appeared at critical periods of life, for the age incidence of macular dystrophies was found to extend over a continuous unbroken range. The conception that these lesions are purely macular was shown to be too rigid, for in many cases considerable extension beyond the central area could be observed in longstanding cases. Moreover sharply defined peripheral and central lesions may be present in combination (Sorsby, 1941).

The present study based on five families brings out the existence of a genetic affection which manifests itself at about the age of 40 years. In the early stages there is oedema and a haemorrhagic-exudative reaction in the central areas; this progresses unto atrophy centrally, generally with some choroidal sclerosis and heavy pigmentation; ultimately the whole of the fundus shows a diffuse atrophic reaction. The affection is inherited as a simple dominant. It therefore establishes the existence of a haemorrhagic type of macular dystrophy, and confirms the view that macular dystrophies cannot always be regarded as localised lesions, but are occasionally, and possibly frequently, merely the starting point of a diffuse retinal or choroidal disturbance.

I. CASE RECORDS.

1. *The Randall family.*

(Pedigree Plate 1 and Figs. 1-5).

(1) MISS MARY RANDALL (IV, 1 *in pedigree plate I*), aged 39 years when first seen in May, 1946. Her vision in the right eye was 6/60 and in the left 1/60. Three years previously Mr. H. M. Armstrong, of Bedford, had found vision of

6/6 in the right and 6/12 in the left. The left fundus at that time showed a pale oedematous central area with a small haemorrhage on its outer side. An intensive general examination proved negative, and early in May, 1946, the patient was again seen by him as vision of the right eye had become blurred. The fundus appearances in this eye were now identical with those observed in the left three years previously. The picture in the left eye had changed considerably meanwhile; the central area had become largely scarred, as can be seen from Fig. 1*b*. The changes in the right eye became more marked during the course of the succeeding two months. Fig. 1*a* shows that by July, 1946, the oedema had spread to involve the disc so that the picture was now one suggestive of neuro-retinopathy showing oedema, haemorrhages and exudates. Observed frequently since May, 1946, the changes in the left eye have not progressed to any extent, whilst those in the right eye are now (22 months later) assuming the appearances of atrophy (Fig. 1*c*). This patient's peripheral fields are full. Colour vision is good and there are no subjective symptoms of night blindness, or of poor dark adaptation. A provisional diagnosis of macular dystrophy of the exudative type made by Mr. Armstrong seemed reasonable, particularly in view of the family history. The patient held that the affection had appeared in her family over three generations, always coming on at about the age of 40. She stated that the women in her family are apt to be more severely affected than the men, and did not readily accept an assurance that there was no danger of blindness as distinct from central loss of vision. A full investigation of the family, which originally hailed from Bedfordshire, but is now scattered in that county, Northamptonshire and the South of England, was made possible by her ready collaboration.

Plate I shows the pedigree which extends over five generations with observed cases in the second, third and fourth generations. There is only presumptive evidence of the affection in the first generation, whilst the members of the fifth are all too young to show the affection. In Miss Randall's generation (the fourth) there is only one other affected member as yet, a second cousin, Mr. John Pritchard.

(2) JOHN PRITCHARD (IV, 24) is now aged 44 years. He was seen 15 months ago, when his vision was 6/6 each eye and the fundi were normal. Six months later he came complaining of sudden blurring of sight in the right eye. Vision was down to 6/36 in this eye, and ophthalmoscopically the picture was identical to that first observed in the case of Miss Randall. There was a central oedematous area with temporal and also nasal haemorrhages. The disc and vessels were normal. His fields were full and colour vision was good. He had not experienced any symptoms suggestive of night blindness throughout his life. Unfortunately it has proved impossible to follow him up.

In the generation antecedent to these two patients five affected members were observed personally by one of us (A.S.). Records concerning two more have been obtained from Mr. E. H. Harries-Jones of Northampton, whilst three more who are now dead are reputed to have been affected. The sub-joined case histories 3-12 give the details concerning this generation.

(3) MRS. MABEL PRITCHARD (III, 12), the mother of J. P. (No. 2 above and IV, 24 in pedigree), aged 67 years. Her trouble started at the age of 40 years and has progressed slowly. Vision is 6/36 partly in each eye. As can be seen from the fundus drawings (Figs. 2*a* and 2*b*), there are massive pigmentary changes in both eyes extending well beyond the central area, particularly in the left eye. Apart from the pigmentary changes, there is a suggestion of patterned exudate on the nasal side of the right disc and peculiar "woolly" massive exudates temporally. In both the right and left fundi the choroidal vessels in the central

area are exposed, and there is a suggestion of incipient choroidal sclerosis. This patient, too, has not been conscious of any night blindness, and her colour vision is good.

(4) MRS. AMY MARTIN (III, 16). Aged 68 years, her fundi are not markedly dissimilar from those of her cousin, Mrs. M. P. (III, 12). The same massive pigmentary changes and patterned exudate are present, but there is also undoubted evidence of central choroidal sclerosis. Towards the periphery the choroidal vessels are exposed, but not definitely sclerosed. Vision is 6/60 in each eye. First symptoms developed at 41. She gets about freely, and by the aid of a magnifying glass can read big type. Fig. 3 shows the fundus of the right eye. The left (not drawn) is very similar.

(5) ALFRED RANDALL (III, 6), a member of the sibship including patients Nos. 5 to 9 (III, 6, 4, 3, 1 and 2 respectively), was seen in 1937, when drawings were made of his eyes (Figs. 4*a* and 4*b*). Vision was reduced to hand movements in each eye. His sight had failed at the age of 43 years and steadily got worse. At the time of examination, when he was 56 years, he could readily find his way about London. He died a year later from lymphatic leukaemia. His peripheral fields and colour vision were good. Both fundi showed extensive choroidal atrophy in the central and pericentral areas. There was much pigmentary reaction in the affected area and unmasking of the choroidal vessels peripherally. Distinct choroidal sclerosis on the temporal side of the right disc was present.

(6) MRS. ANNIE THORNTON, aged 71 (III, 4). This patient is totally blind. A full examination proved impossible. Twenty years ago she had trephine operations on each eye—apparently not for glaucoma, but for the relief of failure of sight, which began at about the age of 40 years. There is some post-operative iritis. An incomplete view of the fundus revealed an almost totally white background with massive pigmentary changes and narrow retinal vessels. The discs were somewhat pale, but showed no evidence of glaucomatous atrophy. Tension in each eye was normal. Fundus drawings could not be obtained, but the appearances are very similar to those seen in her sister, Mrs. E. C. (III, 3).

(7) MRS. ELIZABETH CLARK (III, 3). A frail old lady of 77 years, suffering from chronic glaucoma, which has not been treated. Her sight began to fail at about the age of 40 years and has deteriorated steadily. Fig. 5 shows the fundus of the left eye. Apart from glaucomatous atrophy, there is obvious choroidal sclerosis peripherally, and almost total atrophy of the choroid and retina centrally with massive pigment proliferation.

(8) and (9) JOHN RANDALL AND GEORGE RANDALL (III, 1 and 2), two elder brothers of the last three patients. Both these are now deceased. The elder of these two brothers was the father of our first patient. He died aged 67 years, and could see to get about the country until the end of his life. His trouble began at the age of 40 years, and he had to retire from business at the age of 52 years owing to "centre blindness." He was seen during the first world war by Mr. Harries-Jones, who found a central haemorrhage in one eye, followed in about two years by the same condition in the other. The younger brother (III, 2) was known to Mr. Harries-Jones as likewise affected.

(10), (11) and (12) (III, 7, 9 and 14). The three deceased members of this generation concerning whom only hearsay evidence is available.

ROSA RANDALL (III, 7) is reported to have died blind at about the age of 70 years. Her trouble began at about the age of 40 years and progressed steadily.

JOHN RANDALL (III, 9) died at the age of 57 years. His sight is stated to have been "slightly affected" from "centre blindness."

FLORENCE O'HARA (III, 14) died aged 72 years. She is reported to have "lost central sight" at 42 years, but could always see to get about.

In the generation antecedent to this, one member (II, 3) was observed by Mr. Harries-Jones, and two more are reputed to have been affected. These patients (13-15) are now all dead.

(13) GEORGE RANDALL (II, 3) is reported to have developed "centre blindness" at the age of 40 years. He lived until the age of 72 years and could "see

sideways." He used to get about comfortably in the village in which he lived. Mr. Harries-Jones writes concerning this patient: "I saw him about forty years ago at a doctor's surgery with very poor light, and found both retinae covered with pigmentary degeneration, and central vision practically nil."

(14) RICHARD RANDALL (*II, 4*). *His daughter, Mabel (III, 12), states that his* "central sight" went at the age of 40 years.

(15) MRS. SARAH BUTT (II, 5). Her daughter, Amy (III, 16), states that her mother became affected at the age of 48 or 49 years, when "her central sight went." She died at 65 years and was "four-fifths blind."

Concerning the first generation all that is known is that John Randall died late in life and had "perfect sight": his wife died at the age of 40 and was not known to be affected. A brother of hers, who survived to old age, is said to have been affected. Apart from the eye lesions this family is remarkably free from general disturbances, and in particular from cardiovascular and neurological affections. There is no instance of consanguineous marriages in this group.

Reconstructing the essential features of the affection as seen in this family the following points emerge:

(1) A fundus lesion has been observed over three generations. Transmission is not sex-linked, and the mode of inheritance fits in well with a simple autosomal dominant. This is shown by the following *analysis*:

Number of individuals aged 40 years and over.

	Unaffected			Affected		
Generation	M.	F.	P.	M.	F.	P.
II	1	2	3	2	1	3
III	2	3	5	4	6	10
IV	1	2	3	1	1	2
V	0	0	0	0	0	0
	4	7	11	7	8	15

(2) The affection begins at about the age of 40. Subjectively the first sign is blurring of vision. Objectively the course of the affection extends from a localised oedema of the central area associated with haemorrhages to a terminal phase in which choroidal vessels disappear and massive pigment proliferation is seen against a white background. Figures 1 to 4 show the successive stages beyond the initial slight and localised oedema at the macula. Figs. 1*a* and 1*b* illustrate the appearances in the same patient in whom there was a time lag of three years between the left and right eye: Fig. 1*c* shows the condition depicted in Fig. 1*a* after two years. Figs. 2*a* and 2*b* illustrate considerable extension

beyond the central area with exposure of the choroidal vessels, proliferation of pigment and the presence of woolly exudates in the patient in whom the affection had run a relatively mild course over 27 years. Fig. 3 shows a still further extension of the process with clear choroidal sclerosis. The time factor is approximately the same as in the preceding patient. Figs. 4*a* and 4*b* represent the fundus appearances after the affection had existed for some sixteen years. Here central vision was rather more affected and choroidal atrophy rather than choroidal sclerosis is evident. The lesion is still largely central, but though more localised and of lesser duration would appear to be more intense than in the preceding two patients. Fig. 5 may be taken as representing the terminal state: the choroidal vessels have disappeared centrally and are sclerosed peripherally. There is no suggestion of any haemorrhages or exudates, but massive pigment proliferation is present.

(3) The histological nature of the affection is dubious. The first objective signs would suggest a central retinal lesion. The intermediate and terminal stages indicate that the lesion is primarily choroidal. It is possible that the apparently retinal lesions first seen are the result of the slow cutting-off of the choroidal blood supply to the central area of the retina from underlying choroidal sclerosis.

(4) The available evidence therefore points to a genetic affection of a simple dominant mode of inheritance, beginning at about the age of 40 with a picture simulating central retinitis or possibly neuro-retinitis. The prognosis is, however, more serious than in a macular dystrophy, for in the course of time the whole of the fundus is involved from sclerosis and ultimately disappearance of the choroidal vessels. Though there is some variation in the rapidity of progress in different members of the family, it may be taken that blindness ensues in the course of thirty years or so.

2. *The Carver family.*

(Pedigree Plate II and Figs. 6-15).

In this family—mostly resident in Cumberland—affected members have been observed over two generations by one of us (M. E. J. M.). As can be seen from pedigree plate 2 there is a history that two more antecedent generations were likewise affected. The surviving members of the fifth generation are all below middle age. Twenty-seven members of the third and fourth generation of this family over the age of 40 years have been examined and 14 were found affected. All but one patient (IV, 35) dated their trouble to round about the age of 40. None of the

affected individuals is the offspring of consanguineous parents. The condition is known in the family as the "Carver eye" after the male member of the first generation. The family holds that only blue-eyed members are affected.

Fundus drawings (M.E.J.M.) of ten patients are available. For the sake of convenience four groups in this family may be described separately.

(a) Anthony Hepburn and his children (III, 3 and IV, 8-16).

(1) ANTHONY HEPBURN, aged 75 years. First noticed deterioration in vision at about 42 years. Objects appeared to be distorted. Now vision is hand movements at 1 ft. in each eye. As can be seen from Fig. 15, the fundus of the right eye shows a white reflex with some exposed choroidal vessels and scattered gross pigmentation, the latter being especially marked centrally. The retinal arteries are somewhat narrowed. The fundus of the left eye is essentially similar.

There are 4 sons and five daughters all of whom were examined: three sons and two daughters were found affected. (Patients Nos. 2-6 below.)

(2) NELLIE, aged 52 years, married Bedford (IV, 8). She had no trouble until about four years ago, when she began to notice that, despite correct glasses, she could not read. She is able to get about but has little central vision. R.V. 1/60, L.V. 2/60. As can be seen from Fig. 10, which shows the left eye, the macular area is heavily pigmented, surrounded by a white area of choroidal atrophy. At about the macula itself there is an oval red area, probably a hole. There is a small area of choroidal atrophy with exposed vessels below the main patch. The fundus otherwise looks reasonably healthy. Appearances in the right are only slightly less marked; there is, however, no suggestion of a hole at the macula.

(3) ARCHIE HEPBURN, aged 50 years (IV, 9). At the age of 48 years he noted that objects became much smaller in appearance and that blues were confused with greens. R.V. 6/18, L.V. 6/18 part. No defects in colour vision. As can be seen from Fig. 11, there is a generalised atrophic-looking fundus somewhat simulating retinitis pigmentosa sine pigmento. There are fine scattered pigment spots in the macular areas and there are peripapillary groups of small white spots along the upper branches of the retinal vessels, themselves rather narrow. The choroidal vessels show clearly at the periphery.

(4) JOHN HEPBURN, aged 47 years (IV, 10). The right eye has 6/6 vision and the fundus appears normal. The left eye is stated always to have been divergent, and the fundus shows a central atrophic and pigmentary lesion (Fig. 7).

(5) MARGARET HEPBURN, aged 46 years (IV, 11). Has not noticed much wrong with her vision. Both maculae show moderately fine pigmentation.

(6) JIM HEPBURN, aged 44 years (IV, 13). A few months ago he began to notice that he could only see part of an object with his left eye. Vision has gradually become worse so that he is now unable to follow his occupation. R.V. 2/60, L.V. 2/60. Definite paracentral scotomata. The right fundus shows a large atrophic area in the macular region (Fig. 9). There is some fine pigmentation, mainly marginal, and the choroidal vessels are exposed in this area. To the temporal side of this atrophic patch is a small jagged intensely red patch, probably a small haemorrhage. Otherwise the fundus looks healthy. There is a similar, but somewhat larger, patch of atrophy in the left macular area; this patch shows pigment centrally as well as at the margins.

(b) Mrs. E. Lace and her daughter, Mrs. S. Hayes (III, 8 and IV, 20).

(7) MRS. ELLEN LACE, aged 74 years (III, 8). Vision began to deteriorate at about the age of 45 years, and is now hand movements at 2 ft. Her fundi show massive central and peripapillary choroidal atrophy of a gyrate type. There

is considerable pigment disturbance. Peripherally the choroidal vessels are exposed and there are numerous atrophic areas (Fig. 14). She is not myopic.

(8) MRS. SARAH HAYES, aged 54 years (IV, 20). About 8 years ago (though probably earlier) her sight began to deteriorate. Vision with small minus correction is right 6/18, left 6/24. The whole of the fundus is "thinned" and patchy with fine and scattered muddy-looking areas (Fig. 13). There is peripapillary choroidal atrophy, not clearly delineated from the surrounding retina. The macular area is "muddy" with some fine pigmentation. The retinal arteries are narrowed.

(c) John Batey Murray (III, 19), his brother, Dryden Murray (III, 21), his sister, Jessie McLean (III, 23), and Dryden Murray's son, Jim (IV, 37).

(9) JOHN BATEY MURRAY, aged 78 years (III, 19). The third member of a sibship of eight, of whom three are known to be affected and two more reputed to be so. He himself has never complained of his sight, and would not admit any visual defect. His fundus lesion (Fig. 8) was discovered during the routine examination carried out for this study. Vision is about 6/18 in each eye. The fundi show fine scattered pigment in the macular area, with patches of choroidal sclerosis in the perimacular and peripapillary areas. The rest of the fundus appears healthy. The retinal vessels are normal.

(10) DRYDEN MURRAY died in 1941 at the age of 73 years (III, 21). His sight began to fail at about the age of 45 years, and in 1940 he had only perception of light. There were some slight lens opacities and the fundus showed massive choroidal atrophy, some choroidal sclerosis and gross pigmentation occupying the whole of the central and peripapillary areas. The retinal vessels were somewhat narrow. Unfortunately no drawing was made.

(11) JESSIE MCLEAN, aged 71 years (III, 23). Sight began to fail at about the age of 40 years. Seen when aged 69 years, there was absolute glaucoma in the right eye. The left had perception of light only. The fundus showed massive choroidal atrophy centrally reaching out to the periphery with coarse pigmentation. Six months later she developed an attack of acute glaucoma in this eye, which also went on to absolute glaucoma.

(12) JIM DRYDEN MURRAY, aged 50 years (IV, 38), the son of Dryden Murray (III, 21). At the age of 36 years he began to notice that objects looked distorted with the left eye. The appearances observed four years later by Dr. J. A. Ross, of Carlisle, are depicted in Fig. 12*a*. A heavy exudative and atrophic reaction is present centrally. The same symptoms developed in the right eye two years later. Fig. 12*b* shows the fundus of the right eye at the present; the left eye is rather less heavily involved. In both fundi the whole background shows degenerative changes, most marked in the central areas. At the macular and the peripapillary areas the choroidal vessels are exposed, with evidence of sclerosis. Extensive pigmentary changes are present. Vision is grossly affected in the periphery as well as centrally.

(d) Two further observed members, Annie Kirkpatrick (III, 11), and her nephew, John Ernest Murray (IV, 36).

(13) ANNIE KIRKPATRICK, aged 65 years (III, 11). The patient has been short-sighted since childhood, but has not been able to obtain suitable glasses for some indefinite time. She has a moderate degree of myopia with astigmatism. Her fundi are similar in appearance to that of Anthony Hepburn (III, 3), illustrated in Fig. 9, though the condition is not quite so advanced.

(14) JOHN ERNEST MURRAY, aged 59 years (IV, 36). His mother, Ann Tyson (III, 17), died at about the age of 80 years. She is reputed to have been unaffected. (Her brother, John Batey Murray (III, 19), was also reputed to be unaffected, but was found affected on examination.) John Ernest Murray noticed deterioration in vision when he was aged 18 years, but served in the Army during the first world war. He states that his vision has not deteriorated since the age of 26 years. Vision in each eye is 6/18 and the fields are full. Fig. 6 shows the condition of the right eye. The left is similar. There is fine pigmentary disturbance and some few light-coloured whitish spots in the central area.

The essential features in this family are:

(1) A fundus lesion observed over two generations with a history of the affection in the two antecedent generations. As can be seen from Pedigree Plate II the mode of inheritance fits in well with a simple autosomal dominant. This is shown by the following analysis:

Number of individuals aged 40 years and over.

	Unaffected			Affected		
Generation	M.	F.	P.	M.	F.	P.
II*	1	1	2	4	2	6
III†	4	4	8	4	6	10
IV	3	7	10	5	4	9
V	0	0	0	0	0	0
	8	12	20	13	12	25

* On the assumption that II, 6 was affected, though recorded (on the history) as unaffected.

† On the same assumption for III, 17.

(2) With the exception of one patient (IV, 36), who dates his lesion to the age of 18 years and records no further deterioration after the age of 26 years, the patients all developed the affection at about the age of 40 years. In one instance—IV, 9—symptoms did not appear till the age of 48 years.

(3) The range of ophthalmoscopic appearances is rather more limited than that seen in the Randall family. The earliest stages—an oedematous-exudative reaction at the macula—have not been observed here. The intermediate stages of a pigmented macular lesion with exposure of choroidal vessels in the earlier forms and more extensive changes with atrophy—or possibly exudative reactions—in the somewhat later forms, are illustrated in most of the patients in the fourth generation. (Figs. 6, 7 and 9-13). For the preceding generation Fig. 15 may be taken to represent not only the patient to whom it refers, but also patients III, 21, III, 23, and III, 11. A milder course is observed in III, 8 and one still milder in III, 19. (Figs. 14 and 8.) Another exceptional feature in this group is that one patient (IV, 10) though already aged 47 years shows a lesion in only one eye (Fig. 7).

(4) Taken as a whole this family shows close parallels to the Randall family in so far as it gives the same mode of inheritance, an apparently similar lesion in the macular region, the same spread peripherally with exposure of the choroidal vessels, and

ultimately the same disappearance of these vessels leading to subtotal blindness.

3. *The Ewbank Family.*

(Pedigree Plate III and Figs. 16-18).

In this family the affection has been observed over two generations. The family is resident in London and the Home counties.

(1) RICHARD EWBANK (II, 7) died blind at the age of 74 years. He had been a patient of the late Mr. R. P. Brooks, from whose case records it appears that he was treated for "maculitis." His trouble began at about the age of 43 years, and according to his son he was soon unable to read, but always retained some sight, *e.g.*, could play cards, do some gardening and go about unaccompanied.

(2) MAURICE EWBANK (III, 10), aged 48 years. Seen by one of us (N. G.) in 1942, when he was 42 years of age. Vision with small minus correction was 6/6 in the right eye and 6/60 in the left. The left macula at that time showed mottling, apparently of recent onset. The right fundus was normal. Three years later the right eye had become "troublesome"; mottling of the macula was now present, with slight pigmentary changes at the upper border of the macula. The changes in both the left and right fundi have progressed steadily, and the present appearances are depicted in Figs. 16*a* and 16*b*. Definite choroidal sclerosis is present on the macular side of both discs, more marked in the left eye than in the right. In the right eye, which still has vision of 6/9 partly, the macula is mottled with some slight pigment reaction, and the choroidal vessels are exposed in the perimacular area; white dots are seen more peripherally. The appearances in the left eye are more marked, and both choroidal sclerosis and massive pigmentary changes are present centrally. There is considerable unmasking of the peripheral choroidal circulation with white dots, mainly equatorial in position. Colour vision, as tested by Ishihara plates, is good. There are no subjective symptoms of night blindness.

(3) COLIN EWBANK (III, 11). Died in 1947 at the age of 46 years, apparently from tumour of the kidney. Symptoms developed at the age of 36 years, when Mr. Brooks found "central maculitis and neuro-retinitis." Vision was then right 6/5, left 6/9. Within six months it had declined to 6/18 part in the left eye. Seen by one of us (N. G.) in 1940, vision then was 6/36 partly in the left eye and 6/6 in the right. He complained that objects seen with the right eye now appeared distorted. Ophthalmoscopically there was a scar at the left macula and oedema at the right. When seen nine months later there was a haemorrhage at the right macula. Vision was deteriorating and was 6/18 two months later, and 6/60 four months subsequently. Sclerosis of the choroidal vessels could now be observed in the right central area. When last seen, towards the end of 1946, pigmentary disturbances towards the periphery were present.

(4) MRS. MARY WATERER (III, 12), now aged 43 years. Was seen at the age of 35 years, when vision was 6/6 in each eye, and the fundi showed glistening "colloid" bodies around the disc and macula. There were no subjective symptoms. In September, 1945, when she was 40 years of age, she came complaining that tiles did not appear straight. Vision in the right eye was 6/6 and in the left 6/9. The left macula appeared swollen, suggestive of an acute toxic choroiditis. Two years later haemorrhages and scar formation were present in the left central area, and vision in the left eye had declined to 6/60. The appearances now, one year subsequently, are shown in Figs. 17*a* and 17*b*. It will be seen that extensive "colloid" bodies are present around the disc, extending to well beyond the equator in both eyes. The right macula appears normal, whilst the left central area shows gross scarring and pigmentation. Vision in the right is still 6/6. The Ishihara test shows colour vision to be good. There is no history of night blindness.

(5) MRS. KATHLEEN HUGHES (III, 13). The daughter of Richard Ewbank by

his second marriage. She is now 41 years of age and was first seen nine years ago because of loss of vision in the left eye. The right fundus was then normal. The left showed oedema at the macula with small haemorrhages and scattered pigment; vision was 6/60. Over the course of a year the haemorrhages in the left absorbed slowly, but there was no return in vision. The right eye remained normal till 1945, when she was 38 years of age. Pigment changes were now present in the central area with a haemorrhage below the macula, and four months later there was a definite scar. The appearances now are shown in Figs. 18*a* and 18*b*. In the left eye there is chorio-retinal atrophy in the central area with a veil-like scar and gross pigmentation, whilst in the right eye gross pigmentary disturbances with some choroidal sclerosis and peripheral outlying white dots are present. Vision in both eyes is less than 6/60. Colour vision appears defective (Ishihara test) and there appears to be some night blindness.

(6) MRS. ISABEL JAGGER, aged 61 years (III, 3). The history obtained from her cousin, Maurice Ewbank, was that her sight became affected at the age of 58 years, and that "her present condition is similar to that of her sister, Florence." Seen at the age of 60, in 1947, by Sir Stewart Duke-Elder, she was found to have advanced central choroidal atrophy in both eyes, more marked in the right than in the left.

In the Ewbank sibship there are therefore four affected members in a total of six, the affection having been transmitted through an affected father to children of his two marriages to unaffected individuals. Pedigree Plate III gives further information as regards collaterals in this family. It appears that Richard Ewbank (II, 7) had two affected sisters (II, 3 and II, 5) and that these affected sisters have in turn transmitted the affection to some of their children. (III, 2 and III, 3; III, 5 and possibly III, 4.) The eldest member of the fourth generation is only 32 years of age, and the affection is not known to have appeared in any member of this generation as yet.

The range of ophthalmoscopic appearances seen in this family group covers early and intermediate stages only. Oedema and haemorrhages at the macula have been observed in Colin Ewbank and his two sisters as the earliest lesions. The first observed changes in Maurice Ewbank were mottling of the macula. Scar formation in the central areas have been seen in Colin and in Mrs. Waterer. "Colloid" bodies, widely scattered over the fundi, were the first signs in this last patient, and some white dots are also seen in both Maurice Ewbank and Mrs. Hughes, though in these patients they are probably of later origin. The appearances depicted in Figs. 16 to 18 are very largely those of the intermediate stages. Figs. 18*a* and 18*b* showing the present condition in the youngest member are obviously an earlier stage of the appearances depicted in Figs. 16*a* and 16*b*, which illustrate the fundi of the eldest surviving member. The appearances shown in Fig. 17*a* representing the right eye of the elder sister (III, 12) bear no resemblance whatever to those seen in the other illustrations; they are essentially a representation of widespread "colloid" bodies, but the appearances in her left eye (Fig. 17*b*) show that changes in the central area are fundamentally similar to the lesions seen in the

other members of the family. This widespread distribution of colloid bodies scattered over the fundus is unique, not only in this particular patient in this family, but for all patients recorded in this study. The appearances in Mrs. Hughes (Figs. 18*a* and 18*b*) bear considerable resemblance to those seen in the Randall family (Mrs. Pritchard and Mrs. Martin, Figs. 2 and 3), whilst those observed in Maurice Ewbank (Figs. 16*a* and 16*b*) parallel those seen in the Cranston sibship recorded below (Fig. 26).

It will be noted that the affection began at about the age of 40 years in all the patients in this family, except that in the case of Mrs. Hughes the left eye failed at the age of 32 years, and in her brother Colin at 36 years.

The transmission of the affection by an affected man to the children of two marriages suggests dominant inheritance. The occurrence in collateral branches supports this. Taking the family history on its face value, the following simple analysis emerges.

	Unaffected			Affected		
Generation	M.	F.	P.	M.	F.	P.
II	1	2	3	1	2	3
III	2	2	4	2	5	7
IV	—	—	0	—	—	0
V	—	—	0	—	—	0
	3	4	7	3	7	10

In this family the salient features are therefore :

(1) A fundus lesion observed over two generations in the children of two healthy mothers married to an affected man. The affection is also reputed to have occurred in two sisters of this man and their descendants, one of whom is known to be affected.

(2) In all patients onset was at about the age of 40 years, except that in one patient the first eye failed at 32 years, and in another patient aged 48 years, vision is still 6/9 part in one eye with an extensive central lesion.

(3) Oedema and haemorrhage at the macula were observed as the first ophthalmoscopic changes in at least 3 of the 5 patients. Choroidal sclerosis is an obvious feature in two cases. Widespread "colloid" bodies are a striking aspect in one patient.

(4) None of the patients studied is old enough to show the terminal stage of subtotal retinal and choroidal atrophy.

4. *The Kempster Family.*

(Pedigree Plate IV and Figs. 19-24).

This Hertfordshire family was reported in part in an earlier study (Sorsby, 1940), when it was given as an example of macular dystrophy with intense pigmentary changes. The salient features then recorded were the occurrence of heavy pigmentation in the central areas observed in three sisters aged 62, 60, and 50 years. Another sister, aged 53 years, showed a fundus lesion which bore little resemblance to those seen in the other members of the family; in her case there was an extensive area of peripapillary retinal atrophy with comparatively little pigmentary disturbance and but little central involvement, whilst towards the periphery there was some suggestion of choroidal sclerosis. In these four sisters the affection began at about the age of 40 years. A brother, then aged 55 years, was reported as having developed " slight choroiditis " in the right eye, and " macular choroiditis " in the left eye at the age of 47 years. The history then obtained recorded that the father died " practically blind " at the age of 63 years, his eye trouble having begun at about the age of 40 years; "nearly all his brothers were affected "; the son of one of the brothers was also said to be affected. The four sisters observed had one unaffected sister and four unaffected brothers.

This family has now been re-examined, and Plate IV shows the pedigree. It will be seen that cases have been observed over one generation only, the third. None of the members of the fourth generation has yet reached the age of 40 years. There are no surviving members of the second generation and only hearsay evidence concerning this generation and the antecedent generation is available.

In the third generation of ten sibs four of the five sisters and three of the five brothers are affected.

(1) ARTHUR KEMPSTER (III, 9), aged 52 years. He gives a history that the first trouble began at about the age of 34 years, when he noticed "spots in a blue sky" when looking with the right eye. This apparently did not get worse until about the age of 47 years, when both eyes rapidly failed. The fundi of the two eyes (Figs. 19*a* and 19*b*) are not particularly similar. The left eye shows a mottled macular reaction surrounded by a fairly well defined brown ring, outside which white dots are present. Towards the periphery white exudate-like reactions are present. In the right eye a central pigmented and exudative lesion shows a considerable amount of veil-like scar tissue centrally with a few exudates equatorially.

(2) MRS. ROSE GRAVES (III, 6), aged 50 years when seen in 1939. The right eye failed at about the age of 46 years, the left at 48 years. Her fundi in 1939 are shown in Figs. 20*a* and 20*b*. She now lives in Canada and could not be seen.

(3) MRS. ANN REDDING (III, 5), aged 53 years when seen in 1939. Her eye trouble began at about the age of 40 years. Her fundi at that time are shown in Figs. 21*a* and 21*b*. They were puzzling then owing to the perimacular and peripheral involvement with relatively little central lesion. She died a year after these drawings were made.

(4) JOSEPH KEMPSTER (III, 8), aged 54 years. The right eye was lost in a war injury in 1916. The left eye began to fail at the age of 48 years. Vision is down to 6/60. The earliest stages observed by one of us (N. G.) consisted of oedema. and subsequently haemorrhages at the macula. The present appearances—*six years after onset of trouble*—are depicted in Fig. 22. There is an extensive atrophic lesion centrally with exudate and pigmentary reactions peripherally.

(5) WILLIAM KEMPSTER (III, 4), aged 64 years. This is the brother who was reported to have shown "slight choroiditis" in the right eye, and "macular choroiditis" in the left eye at the age of 47 years. He could not be examined in 1939, and when seen *recently he was dying from cardiac failure.* He was too ill for any drawing of the fundus to be attempted, but a rapid examination showed a fundus lesion not unlike that seen in his sister, Mrs. Poulton (III. 2). Unfortunately an eye for histological examination could not be obtained.

(6) MRS. CAROLINE POULTON (III, 2), aged 69 years. Her sight began to fail at about the age of 40 years. In 1939, when she was 60 years old, her lesion was largely central with fairly heavy patches of atrophy outside the macular area (Figs. 23*a* and 23*b*). *Now the extension peripherally is marked* (Figs. 23*c* and 23*d*). A striking change is particularly noticeable in the right eye where a solid sheath of black pigment spreads from just temporally of the disc across the central area. In addition, there is unmasking of the choroidal vessels and some choroidal sclerosis.

(7) MRS. ALICE HALL (III, 1), aged 71 years. Her sight began to fail at about the age of 42 years. The fundus appearances in 1939, when she was 62 years old, are shown in Figs. 24*a* and 24*b*. *It will be seen that at that time the lesion* was essentially central and consisted largely of a heavy pigmentary reaction, fairly uniform and deep chocolate brown in colour. There was at that time little peripheral extension beyond some whitish dots mainly equatorial in position. Now, nine years later, the extension peripherally is considerable and choroidal sclerosis has become evident (Figs. 24*c* and 24*d*).

Of the three members of the family who are reputed to be normal, Frederick Kempster, aged 66 years (III, 3) was not seen. Eliza Wood, aged 56 years (III, 7) and Robert Kempster, aged 50 years (III, 10) were examined and found normal.

In the antecedent generation, the father, as already noted, died blind, at the age of 63 years, his trouble having begun at about the age of 40 years. It appears that he had two affected brothers and one affected sister; two brothers and two sisters are reputed to have been normal. It is also reported that a son of one of his affected brothers, and a daughter of the affected sister are affected. The information given also records that in the generation antecedent to this, the father and a brother were affected, and that this affected brother had an affected daughter. The essential features in this family are therefore :

(1) A fundus lesion observed in 7 out of 10 sibs. In all of them the affection began in the forties, except that it may have begun at the age of 34 years in one member (III, 9).

(2) There is a history of the affection in two antecedent generations, with direct inheritance on four occasions. There is no history of unaffected individuals transmitting the affection.

The following analysis is given with some reserve owing to the indefinite information on generation II.

Number of individuals aged 40 years and over.

	Unaffected			Affected		
Generation	M.	F.	P.	M.	F.	P.
II	2	2	4	3	1	4
III	2	1	3	3	4	7
IV	—	—	0	—	—	0
V	—	—	0	—	—	0
	4	3	7	6	5	11

The range of ophthalmoscopic appearances in this family extends from observed oedema and haemorrhage at the macula to extensive central and peripheral atrophy of the retina and choroid, but the eldest member of this family has not yet reached the advanced age observed in members of the first two families in whom sub-total retinal and choroidal atrophy was noted. The range of ophthalmoscopic appearances is, however, exceedingly wide. The left eye of Arthur Kempster (III, 9, Fig. 19*b*) is strikingly similar to the right eye of Mary Randall (Fig. 1*c*). The only eye of his brother, Joseph (Fig. 22), is likewise very similar to the fundi of Alfred Randall (Fig. 4*a* and 4*b*) and Gertrude Cranston (Fig. 26) recorded below.

(4) Only one member of this sibship (Arthur Kempster III, 9) complained of nightblindness. On Stilling's tables there was heavy colour defect in the four affected sisters.

(5) Of special significance in this family are the recorded changes observed in two members after an interval of nine years. They show extension of the central lesion towards the periphery. (Figs. 23 and 24.)

5. *The Cranston Sibship.*

(Figs. 25 and 26).

The case records of two sisters, Gertrude and Edith Cranston, were published earlier as examples of central and peripapillary choroidal sclerosis (Sorsby, 1939). In both sisters, then aged 59 and 58 years, there was peripapillary choroidal sclerosis involving the macula and producing heavy pigmentary disturbances. The periphery was clear: the peripheral fields were full and the patients could get about quite well with central vision of 6/60.

(1) EDITH CRANSTON. At the age of 46 years she consulted Mr. F. A. Williamson-Noble for difficulty in reading. Figs. 25*a* and 25*b* show the fundus appearances observed then. There was indefinite haze at the disc margin, and some pigmentary disturbances and haemorrhages in the central areas.

A diagnosis of central chorio-retinitis, possibly of tuberculous origin, was made. Vision with correction at that time was 6/12 in each eye. Seen 10 years later by one of us, the fundus appearances had changed greatly. There was evident peripapillary choroidal sclerosis and gross *pigmentary changes at the maculae* (Figs. 25*c* and 25*d*).

Fundamentally the same lesion was found in her sister :

(2) GERTRUDE CRANSTON, one year younger. Here the fundus lesion was rather *more marked centrally and extended further out* (Figs. 26*a* and 26*b*). The subjective symptoms were identical with those of her sister. Her trouble began *in the early forties, and had progressed steadily.*

The family history elicited at that time (and confirmed recently) showed no consanguinity in the parents and revealed no history of any other affected members. Their father died at the age of 49 years from "fatty heart," and their mother at 64 years from "consumption." Both appear to have had good sight. There were two elder sibs, a sister who died at 46 years of age from "cerebral haemorrhage" and a brother who died at 41 years from "consumption." They, too, appear to have had good sight.

The fundus appearances and late onset of the affection suggested the possibility that the original diagnosis of central and peripapillary choroidal sclerosis may have stressed an aspect of the affection rather than the picture as a whole. Re-examination in 1948 showed considerable deterioration in vision. The two sisters, now aged 69 and 68 years, can no longer go about on their own as their peripheral field has shrunk considerably. The central fundus lesions now show considerable extension peripherally. In both sisters much of the peripapillary choroidal sclerosis has been replaced by choroidal atrophy (Figs. 25*e* and 25*f*; 26*c* and 26*d*) whilst there is considerable extension of unmasking of the choroidal vessels with some sclerosis peripherally. There is, moreover, increase of intensely black pigment at the central areas. Similarity in ophthalmoscopic appearances of Fig. 26 in this sibship with Fig. 4 in the Randall group, Fig. 16 in the Ewbank family and Fig. 22*d* in the Kempster family has already been pointed out.

In this sibship the range of observed ophthalmoscopic appearances therefore extends from the early stage when the lesion suggested a central chorio-retinitis; subsequently there was peripapillary and central choroidal sclerosis, and this has now progressed to extensive central retinal and choroidal atrophy with peripheral exposure and some sclerosis of the choroidal vessels. Though a positive family history showing dominant inheritance is lacking, it must be borne in mind that the father died at the age of 49 years, and that information on preceding generations could not be obtained. This family group appears to begin with these two sisters, and definitely comes to an end with them as they are unmarried.

THE RANDALL FAMILY

(FIGS 1 — 5)

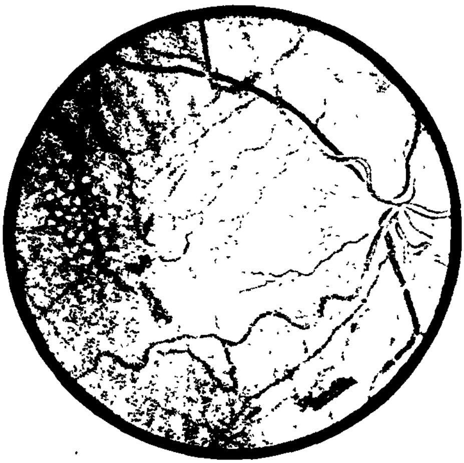


FIG. 1 (*a*)

Miss M. R. aged 41 years. Appearances in the right eye 10 weeks after first onset of subjective symptoms (when patient was 39 years of age). Note swelling of disc, oedema of the central area, haemorrhages and exudates.

FIG. 1 (*b*)

Left eye: appearances 3 years after onset of first symptoms (at 36 years) Note the time interval in onset of symptoms and lesions in the two eyes, and the pigmented proliferating scar in the central area.

FIG. 1 (*c*)

The same eye as depicted in (*a*) 22 months later.

FIG. 2 (*a*)

Mrs. M. P. aged 67 years, a cousin of Miss M. R.'s father. Symptoms first developed about 27 years ago. Right eye. Note gross pigmentary changes, a suggestion of patterned exudates on the nasal side of the disc, the peculiar woolly, massive exudate temporally, and exposure of the choroidal vessels.

FIG. 2 (*b*)

Left eye. Choroidal sclerosis is rather more obvious than in the right eye.

FIG. 3

Mrs. A. M., aged 68 years, a cousin of Miss M R.'s father and also of the patient depicted in Fig. 2. The patterned exudate and choroidal sclerosis are more marked than in the fundi shown in Fig. 2. Symptoms first developed about 27 years ago.

FIG. 4 (*a*)

Alfred R., died at the age of 57 years, an uncle of Miss M. R. Appearances at the age of 56 years, some 13 years after the onset of the first symptoms. Right eye. Note extensive central atrophy and pigmentation.

FIG. 4 (*b*)

Left eye. Appearances are fairly similar to those in the right eye. Note extension of the lesion temporally.

FIG. 5

Mrs. E. C., aged 77 years, the eldest member of the R. family group, an aunt of Miss M. R. Symptoms first developed about 37 years ago. Note extensive central atrophy with pigmentation and fairly advanced choroidal sclerosis peripherally. (There is also coincidental glaumatous optic atrophy).

THE CARVER FAMILY

(FIGS. 6—15)

FIG. 6

John E. M., aged 59 years. His mother (reputed to have been unaffected) was a cousin of Anthony H., depicted in Fig. 15. Right eye: the mildest central lesion observed in this group. Trouble is stated to have begun at the age of 18 without deteriorating since the age of 26. The fundus in the left eye is similar.

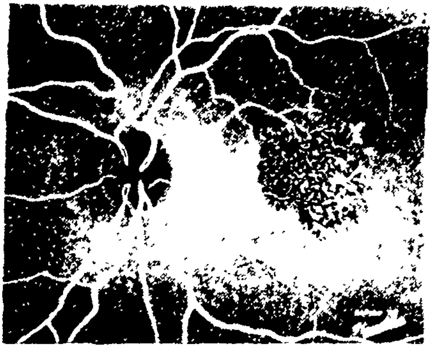


FIG. 7

John H., aged 47 years, a son of Anthony H. The right eye is as yet normal. The lesion in the left is fairly sharply localised to the central area. It is not known when this lesion developed, as the eye is divergent and amblyopic.

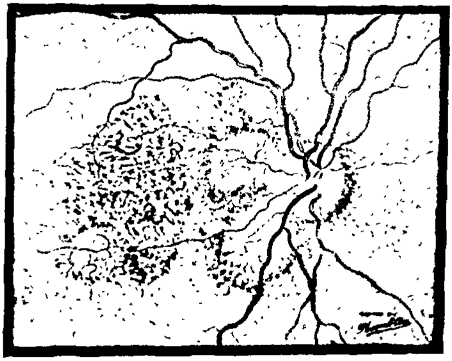


FIG. 8

John B. M., aged 78 years, a cousin of Anthony H, and 3 years older. Patient's vision is 6/18 and he was unaware of any eye trouble. Right eye: there is a fine pigmentary central lesion with considerable patchy choroidal sclerosis. Appearances in the left fundus are essentially similar.

FIG. 9

Jim H., aged 44 years, a son of Anthony H. The right fundus shows a sharply localised lesion with exposed choroidal vessels. Appearances in the left eye are rather more marked. Symptoms began a few months ago.

FIG. 10

Mrs. N. B., aged 52 years, eldest daughter of Anthony H. Note fairly localised central lesion. First symptoms about 4 years previously.

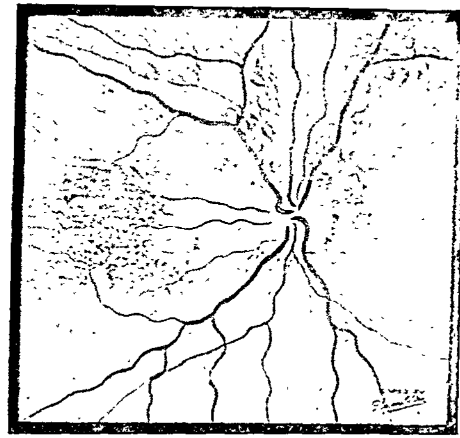


FIG. 11

Archie H., aged 50 years, a son of Anthony H. Right eye: the lesion is more extensive than in his sister, who is two years older. The patterned exudate is particularly striking. The left eye is similar. Symptoms appear to have developed 2 years previously.

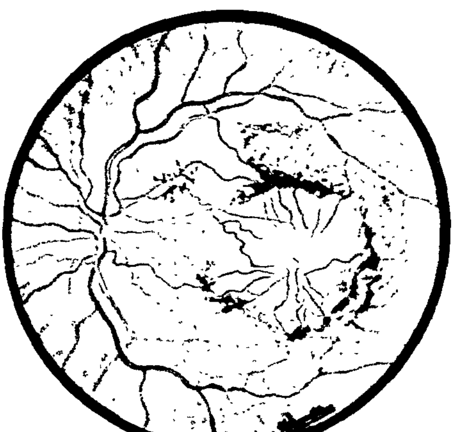


FIG. 12 (*a*)

Jim D. M., aged 50 years. A son of a first cousin of Anthony H. Left eye at the age of 40 years, *four* years after onset of symptoms. There is an extensive exudative-atrophic reaction centrally

FIG. 12 (*b*)

Present appearances of right eye pigmentary changes are present centrally and equatorially. The choroidal vessels are exposed peripherally with some choroidal sclerosis around the disc Appearances in the left eye which failed two years before the right are now fairly similar.

FIG. 13

Mrs. Sarah H., aged 54 years, whose mother, Mrs. Ellen L. (fundi depicted in Fig. 14), is a cousin of Anthony H. Right eye: there is a diffuse "pepper and salt" atrophy of the central areas with fairly well defined macular lesions. The left eye is similar. First symptoms developed about 8 years previously.

FIG. 14

Mrs. Ellen L., aged 74 years, a cousin of Anthony H. and mother of Mrs. Sara H., depicted in Fig. 13. Both eyes show extensive central and peripapillary atrophy with exposure and incipient choroidal sclerosis peripherally. First symptoms developed about 29 years previously. There is no myopia.

FIG. 15

Anthony H., aged 75 years The most severely affected member of the Carver family. Note extensive chorio-retinal atrophy with pigmentation and choroidal sclerosis. Note also similarity to Fig. 5 depicting the most advanced stage in the Randall family. First symptoms developed about 33 years previously.

THE EWBANK FAMILY

(FIGS. 16—18)

FIG. 16 (*a*)

Maurice E., aged 48 years. Right eye. Vision of this eye still 6/9 partly. The macula is mottled, the choroidal vessels are exposed and there is choroidal sclerosis on the temporal side of the disc. There is also a suggestion of patterned exudate peripherally. Symptoms in the right eye began 3 years previously, and 3 years before that, at the age of 42 years, the right fundus was normal.

FIG. 16 (*b*)

Left eye. Symptoms began 6 years previously. Vision is now 6/60. The appearances are essentially similar to those in the right eye, but are more exaggerated. Note similarity to Fig. 25.

FIG. 17 (*a*)

Mrs. M. W., aged 43 years, a sister of Maurice E. At the age of 35 years the vision was full in each eye and both fundi showed a patterned exudate or colloid-like reaction equatorially and peripherally as depicted in the illustration. Right eye: the macula is intact and vision is full.

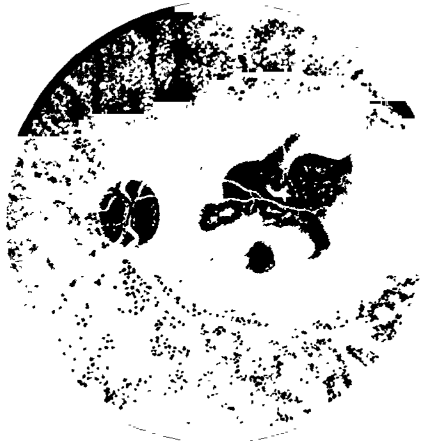


FIG. 17 (*b*)

Left eye : there is a destructive central lesion. Symptoms first began 3 years ago ; the central area was then swollen ; haemorrhages were observed two years later, and vision is now 6/60.

FIG. 18 (*a*)

Mrs. K. H., aged 41 years, another sister of Maurice E. Right eye. Note the pigmentary reactions and choroidal sclerosis centrally with outlying exudates Symptoms in this eye first began 3 years previously. Before that this fundus was known to be normal.

FIG. 18 (*b*)

Left eye. The lesion is more established. Symptoms first began 9 years ago. Note similarity to Fig. 2*a* and Fig. 23*c*.

THE KEMPSTER FAMILY

(FIGS. 19—24)

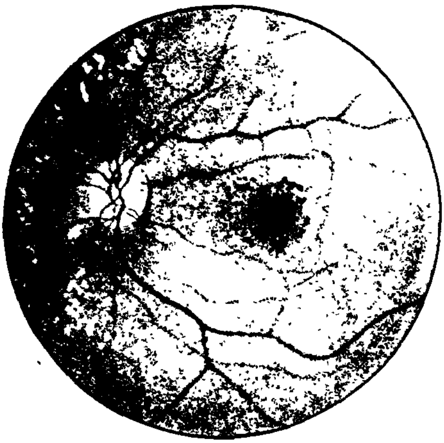


FIG. 19 (*a*)

Arthur K., aged 52 years, the youngest affected brother of Mrs. A. H., whose fundi are depicted in Fig. 24. Left eye: symptoms first began 5 years ago (? 18 years ago). A fairly characteristic macular dystrophy is present with patterned exudate peripherally.

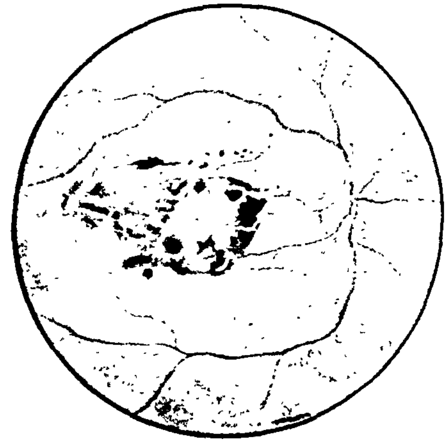


FIG. 19 (*b*)

Right eye: symptoms began 7 years ago. In contrast to the right eye the central lesion does not suggest a macular dystrophy. Note similarity to Fig. 1(*c*).

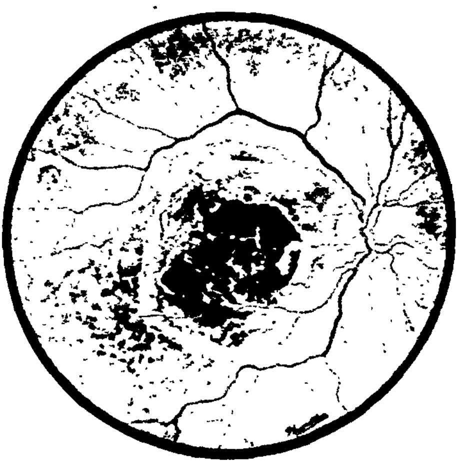


FIG. 20 (*a*)

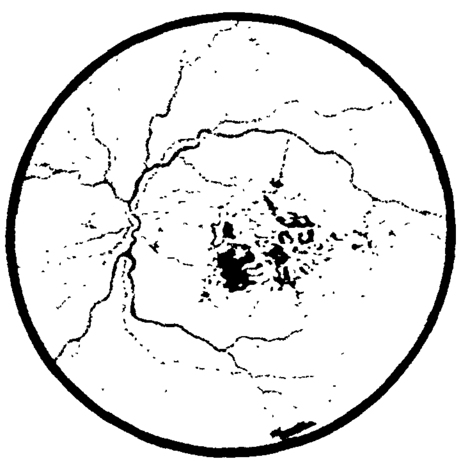


FIG 20 (*b*)

Mrs. Rose G. a sister of Arthur K. Right and left eyes: appearances seen in 1939. The lesions are essentially central, pigmentary in character with choroidal exposure and some retinal atrophy. The present condition is unknown

FIG. 21 (*a*)

FIG. 21 (*b*)

Mrs. Ann R., died aged 54 years, another sister of Arthur K. Right and left fundi: drawn at the age of 53 years. In contrast to the appearances seen in her two elder sisters the lesion was essentially peripapillary rather than central, and extended well towards the equator. Incipient choroidal sclerosis was evident.

FIG. 22

Joseph K , aged 54 years, a brother of Arthur K. Left eye: symptoms first began 6 years ago; the earliest ophthalmoscopic changes consisted of oedema and haemorrhages at the macula. Now there is extensive central atrophy with some patterned exudate and pigment changes peripherally. The right eye was lost in a war injury in 1916. Note similarity to Fig. 4 and Fig. 26.

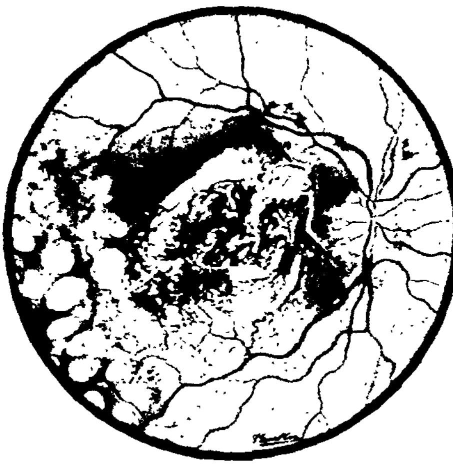


FIG. 23 (*a*)

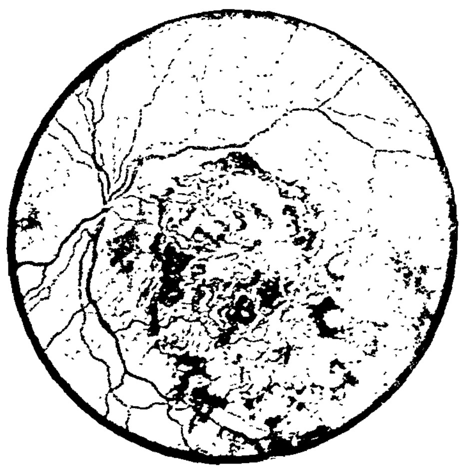


FIG. 23 (*b*)

FIG. 23 (*c*)

FIG. 23 (*d*)

Mrs. C. P., aged 69 years, another sister of Arthur K. Right and left eyes in 1939. (*a*) and (*b*). Note pigmentary reaction centrally with considerable exposure of choroidal vessels, and peripheral extension. (*c*) and (*d*): Right and left eyes in 1948. Note central atrophy, and extension peripherally, and similarity of Fig. 23 (*c*) to Fig. 4 and Fig. 26. Figs. (*a*) and (*b*) show appearances about 20 years after onset of symptoms, (*c*) and (*d*) illustrate the changes 9 years later.

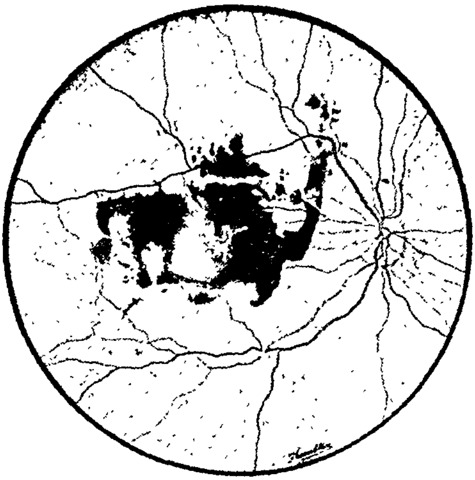


FIG. 24 (*a*)

FIG. 24 (*b*)

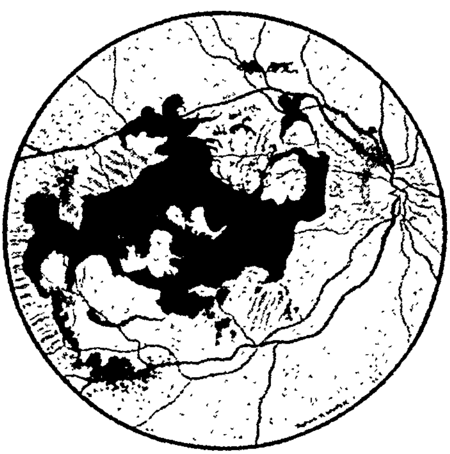


FIG. 24 (*c*)

FIG. 24 (*d*)

Mrs. Alice H , aged 71 years, the eldest member of the Kempster family. (*a*) and (*b*) : Right and left eyes in 1939. There is a gross pigmentary reaction in the central area, with rather more peripheral extension in the left.
(*c*) and (*d*) : Right and left eyes in 1948. There is now considerable extension with exposure of choroidal vessels, more exaggerated in the left where definite choroidal sclerosis is present.
Figs. (*a*) and (*b*) show the fundus appearances 20 years after symptoms first appeared. Figs. (*c*) and (*d*) illustrate the changes 9 years later.

(FIGS. 25 — 26)

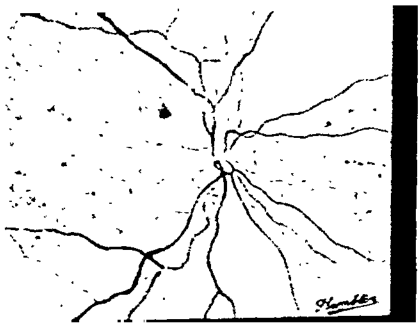


FIG. 25 (*a*)

FIG. 25 (*b*)

FIG. 25 (*c*)

FIG. 25 (*d*)

FIG. 25 (*e*)

FIG. 25 (*f*)

Miss Edith C., aged 68 years, (*a*) and (*b*): Right and left eyes at the age of 46 when symptoms first began Oedema around the disc and in the central area with haemorrhages and pigment reaction were then present. (*c*) and (*d*): Right and left eye: 10 years later choroidal sclerosis and pigmentary changes centrally were marked. (*e*) and (*f*): Right and left 22 years after onset of symptoms. The choroidal sclerosis is becoming replaced by an atrophic reaction. Extension peripherally is considerable.

FIG. 26 (*a*)

FIG. 26 (*b*)

FIG. 26 (*c*)

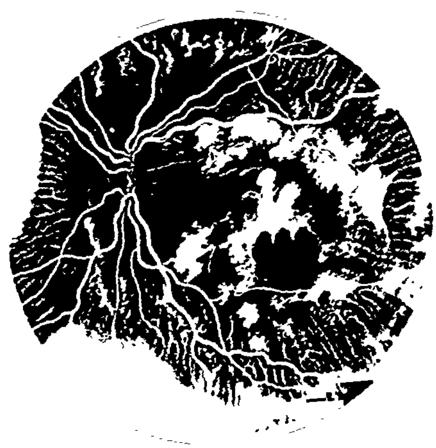
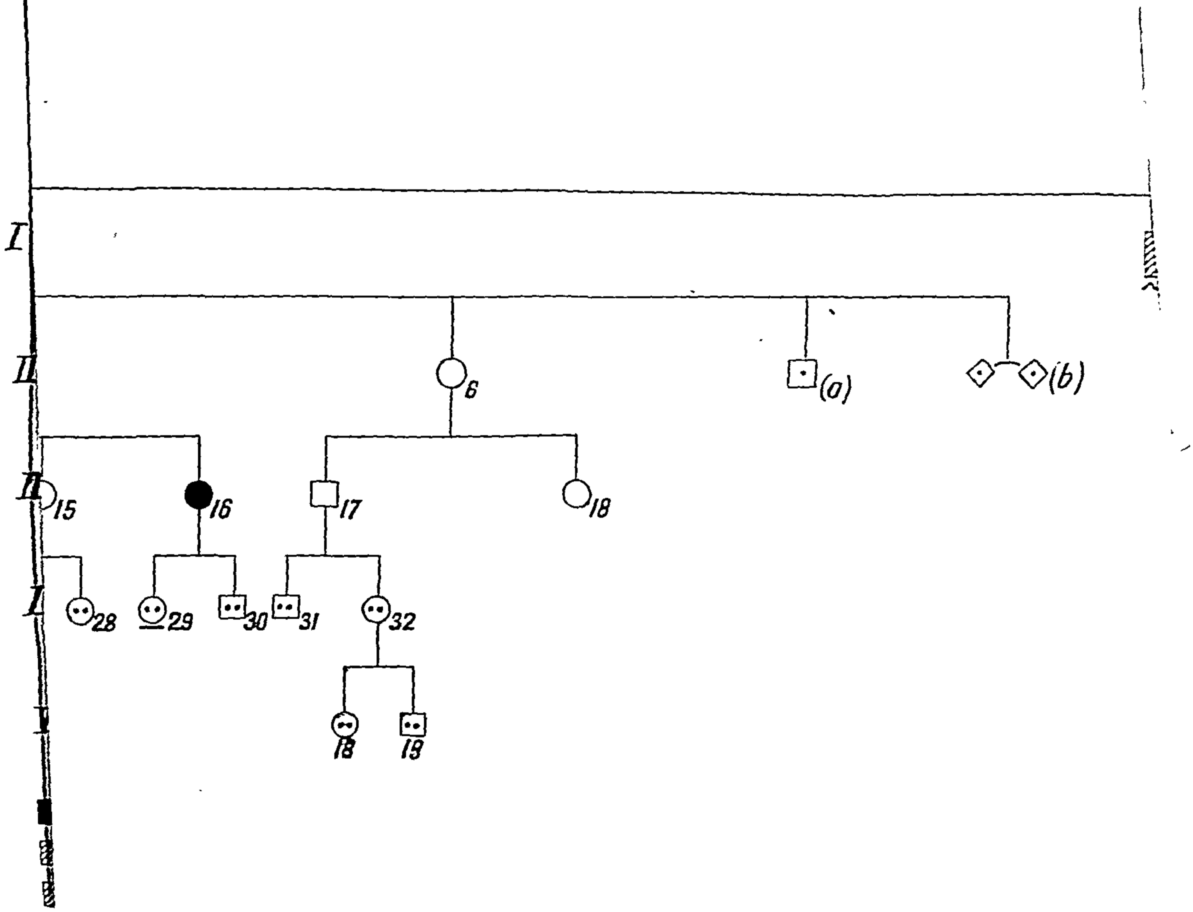


FIG. 26 (*d*)

Miss Gertrude C., aged 67 years, a sister of Miss E. C. (*a*) and (*b*): Right and left eyes in 1939, appearances are fairly similar to those seen in her elder sister 10 years after the onset of symptoms. The duration of the lesion was probably 2 or 3 years longer. (Note similarity to Fig. 4, Fig. 22, and Fig. 23*c*.)
(*c*) and (*d*): Right and left eyes 9 years subsequently. The extension peripherally is marked and the choroidal sclerosis is being replaced by atrophy.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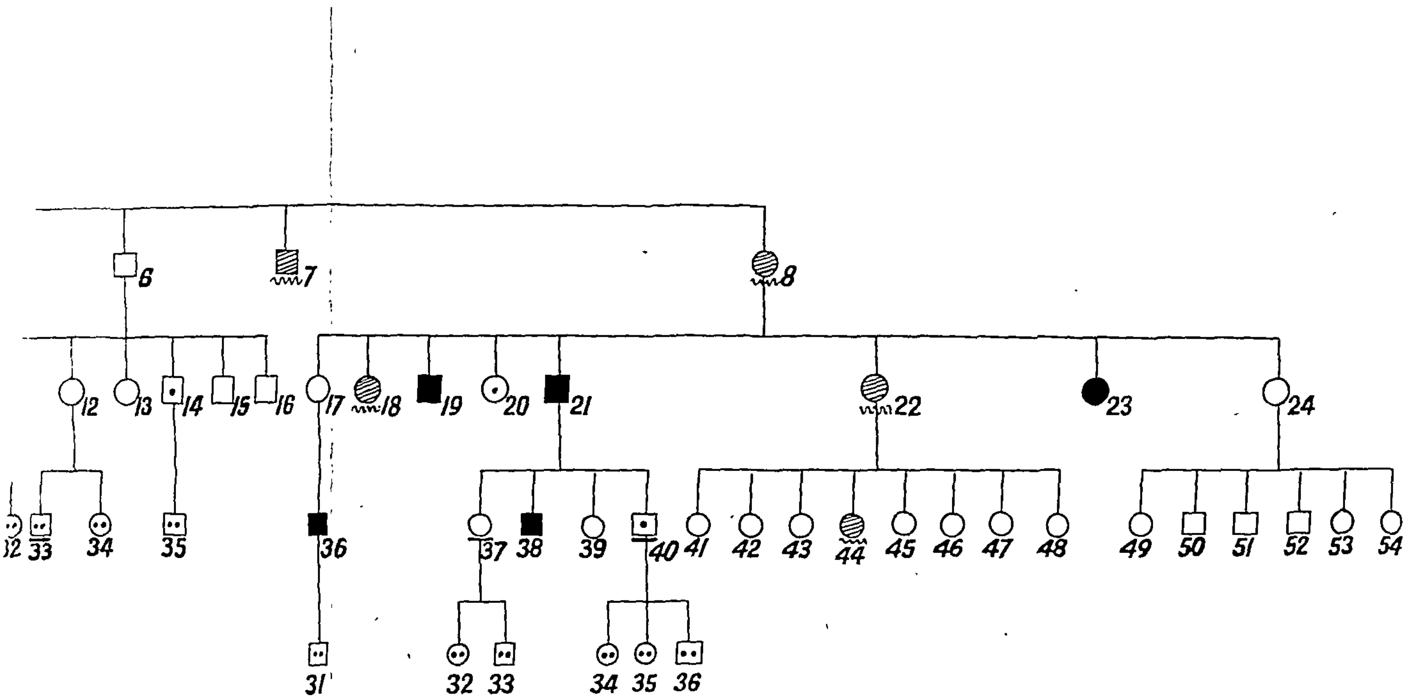

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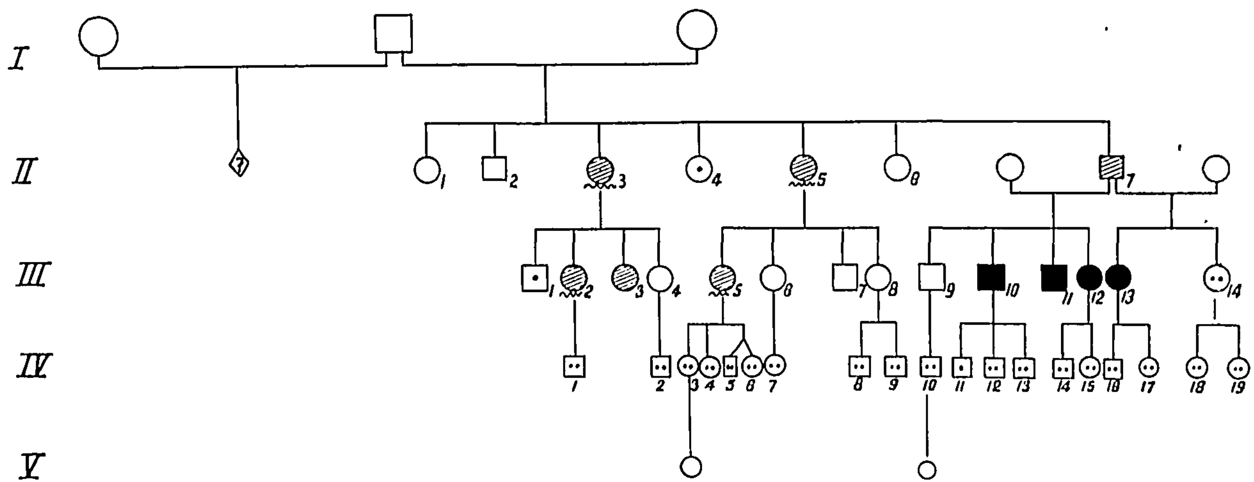
Pedigree Plate III.—*The Ewbank Family.*



=affected, seen.

=reputed affected and found so by the late Mr. R. P. Brookes and by Sir Stewart Duke-Elder. (II, 7 and III, 3 respectively).

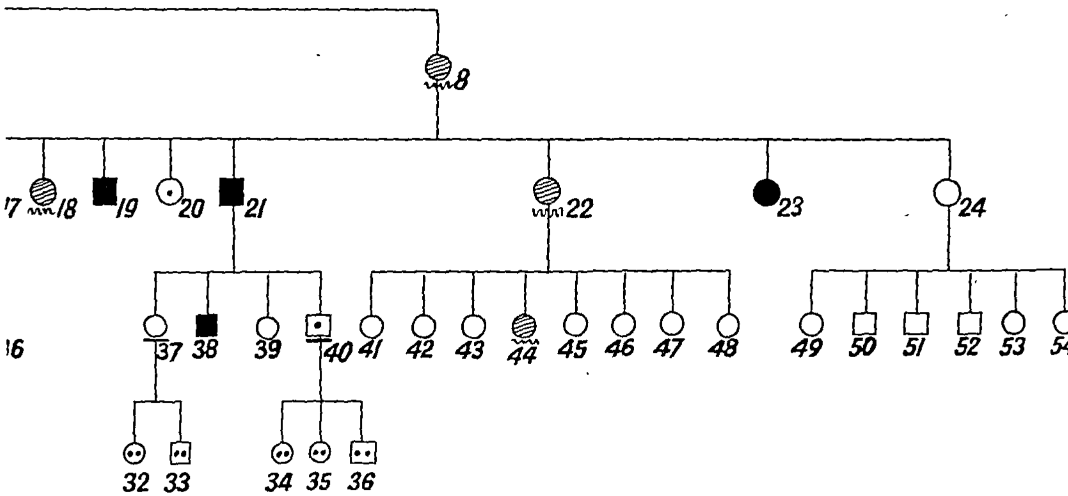
=reputed affected, not seen.

not seen, reputed normal.

=died before reaching the age of 40 years.

present age is under 40 years, not seen.

present age is under 40 years, seen and found normal.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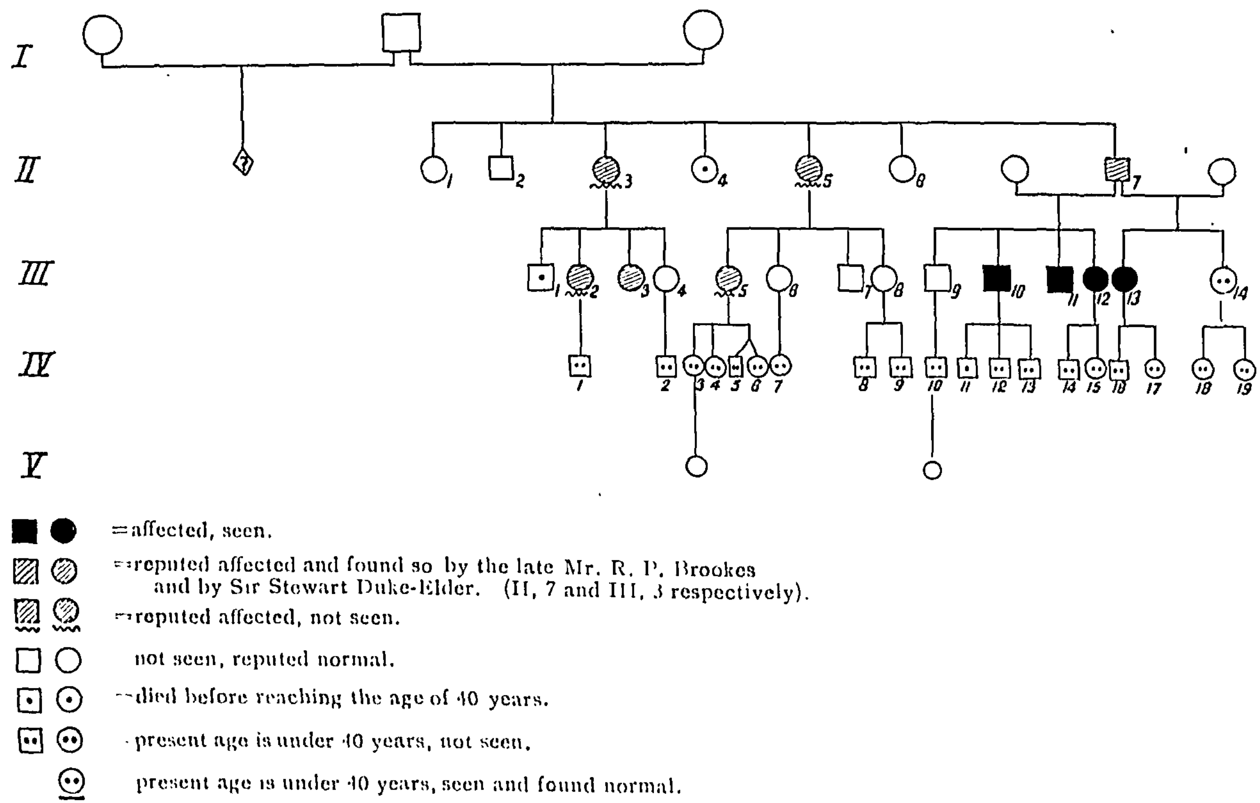
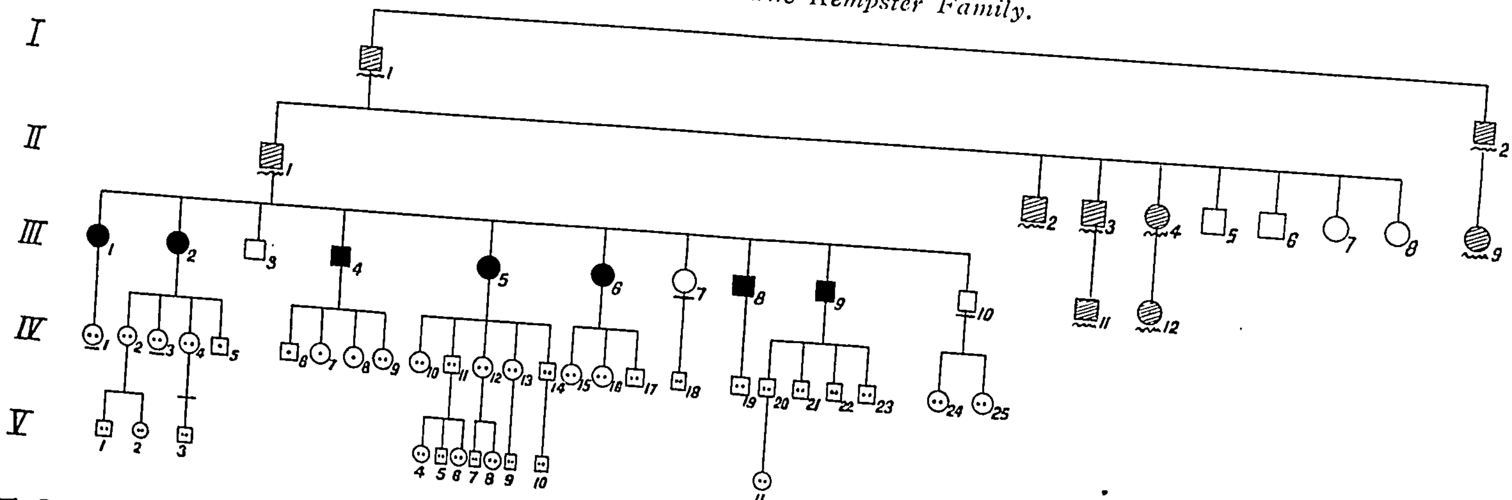
Pedigree Plate III.—*The Ewbank Family.*



Pedigree Plate IV.—*The Kempster Family.*



=affected, seen.

=reputed affected, not seen.

=not seen, reputed normal.

=seen and found normal.

=died before reaching the age of 40 years, not seen.

=present age is under 40 years.

=present age is under 40 years, seen and found normal.

II. DISCUSSION.

1. *Range of fundus reactions.*

Taken individually the appearances seen in most of the members of these five families would present nothing of special interest. The appearances shown in Fig. 1*a* are an almost daily occurrence which might well raise the issue of differential diagnosis between an arteriosclerotic and toxic neuro-retinitis. Those seen in the fellow eye (Fig. 1*b*) might suggest a central choroiditis that has run its course. The appearances in Figs. 2*a* and 2*b* might in turn suggest a diffuse choroiditis, and very much the same applies to those of Fig. 3, where the choroidal sclerosis might be regarded as consequent on an old chorio-retinitis. The appearances in Figs. 4*a* and 4*b* would be more difficult to interpret and are in fact almost identical with those recorded in an earlier study of two sisters showing central and peripapillary choroidal sclerosis. The final picture in the series (Fig. 5) would raise the possibility of advanced disseminated choroiditis.

In the second family the sub-total choroidal atrophy shown in Fig. 15 might raise a differential diagnosis of advanced choroidal sclerosis, atypical retinitis pigmentosa, and possibly disseminated choroiditis. Figs. 6 to 10 on the other hand would be regarded as illustrating a central choroiditis, whilst Figs. 11, 12 and 13 could, with some justification, be regarded as illustrating progressive stages of diffuse choroiditis. The appearances in Fig. 14 would raise the alternative diagnoses of myopic atrophy or gyrate atrophy. As most of these conditions are relatively common, the fundus appearances in individual cases would therefore raise no special diagnostic doubts. Underlying most of these diagnoses would be the assumption of an infective or toxic process, and such treatment as would be undertaken would be directed along those lines.

In the third family the appearances shown in Fig. 16 could pass for an example of choroidal sclerosis. Fig. 17 is more puzzling. The healthy disc and vessels suggest a diagnosis of fundus albi punctatus (Lauber, 1910) rather than retinitis punctata albescens; an alternative diagnosis would be diffuse "colloid" bodies, though the central lesion in the left eye leaves no doubt as to the nature of the affection. Fig. 18 is reminiscent of what has been described as macular dystrophy with heavy pigmentation. In two out of these three cases it is known that the earlier stages consisted of oedema and haemorrhage at the macula.

As for the fourth family, Fig. 19*a* might well represent a macular dystrophy of the mottled type complicated by outlying exudates. The veil-like film over the pigmentary central reaction seen in the left eye (19*b*) is more suggestive of the changes seen in the first

patient of the first family (Fig. 1*c*). Fig. 22 is almost a replica of the appearances shown in Fig. 4. Most of the remaining figures could be regarded as heavy central or diffuse chorio-retinitis.

In the last sibship, Fig. 25 *a* and *b* represent what may be regarded as fairly typical central chorio-retinitis; 25 *c* and *d* have been read to show choroidal sclerosis; whilst *e* and *f* are obvious examples of chorio-retinal atrophy. Likewise Fig. 26 *a, b, c,* and *d* show a similar difficulty in diagnosis.

2. *Implications.*

These considerations emphasise several points:

(1) Gross pigmentary disturbances are not always infective or toxic in origin. Attention to this has already been drawn in the earlier study on macular dystrophies. The present study is further evidence to the same effect.

(2) The earliest changes in a genetic affection may be haemorrhages and exudates identical in appearance with the lesions commonly observed in arteriosclerotic and metabolic disorders. It would therefore seem that as genetic anomalies are studied more intensively, the line of demarcation of the fundus appearances in these affections as from the more widely recognized non-genetic affections is becoming more blurred. The classical teaching that the abiotrophic fundus appearances take the form of the pigment changes of retinitis pigmentosa, atrophy as seen in gyrate atrophy, or macular dystrophy represented by mottling and atrophy, is clearly too limited.

(3) Apart from the wide range of types of reaction that the abiotrophic fundus anomalies may show—mottling, gross pigment changes, atrophy, "colloid" bodies, oedema, exudates, and haemorrhages—there is this significant consideration: these reactions are not all sharply demarcated from each other, but represent different phases in one and the same process. A reaction showing oedema, haemorrhages, and exudates may pass into a grossly pigmented scar and end in an atrophic lesion. The possibility that a particular fundus anomaly may be genetic in character is suggested not so much on the type of reaction—for almost any fundus reaction may be genetic in origin—as by the symmetry of the lesion in the two eyes—and even this criterion does not always hold good, for a genetic lesion may be asymmetrical and for a time unilateral.

(4) A lesion beginning as fairly strictly localised to the central area may extend relentlessly to involve the whole of the fundus. What may appear as a macular dystrophy with its relatively favourable end-result may actually be the starting point of a generalised dystrophy with a gloomy prognosis.

3. *A clinical entity.*

Apart from these general considerations it would appear that the present study also justifies the conclusion that to the relatively small group of clearly defined genetic fundus anomalies there is to be added one more possessing the following features:

(1) *Age at onset.* The affection begins at about the age of 40 years.

(2) *Subjective symptoms.* The first subjective symptoms are blurring of central vision in one eye followed by the same symptoms in the other eye within a matter of months, or perhaps a few years. It is not known whether the two eyes may be affected simultaneously. Central vision rapidly declines, but there is no involvement at this stage of peripheral vision or colour vision. There are no symptoms of night blindness early on or during the course of the affection.

(3) *Objective signs.* Objectively the first signs are oedema, haemorrhages, and exudates in the central area. These progress to scar formation with a varying amount of pigment proliferation, which may be exceedingly massive. The choroidal vessels become exposed and show some sclerosis. Over the course of years the process extends peripherally, choroidal sclerosis generally becomes more manifest and sometimes dominates the picture. During its spread peripherally, exudates—sometimes patterned—may appear and it is possible that widespread glistening " colloid " bodies may be a pointing sign. The end stage is widespread disappearance of the choroidal vessels exposing the sclerotic covered irregularly by proliferating pigment. The terminal stage produces practically total blindness. The polymorphism of the fundus reactions is such that any stage of oedematous and inflammatory fundus lesions as well as diffuse choroidal sclerosis can be simulated.

(4) *Course.* The full course of the affection spreads normally over about 35 years. The process may, however, be milder, or more severe, in individual cases.

(5) *Genetics.* Genetically the condition is probably a simple autosomal dominant.

The following summary table based on the first four pedigrees (excluding the Cranston sibship because of its incompleteness)

Number of individuals aged 40 years and over.

	Unaffected			Affected		
	M.	F.	P.	M.	F.	P.
Randall	4	7	11	7	8	15
Carver	8	12	20	13	12	25
Ewbank	3	4	7	3	7	10
Kempster	4	3	7	6	5	11
	19	26	45	29	32	61

shows the distribution of the affected in relation to unaffected and the sex incidence.

On the expectation of 50 per cent. ratio for a simple dominant, there would therefore seem to be an excess of affected over unaffected. The excess is, however, not statistically significant.

The excess is rather heavier in men. Of 48 men 29 were affected, whilst of 58 women 32 were affected. This excess of men over women is also not statistically significant, nor is it borne out by an analysis of those complete sibships that have been examined ophthalmoscopically. Extracted from the four pedigrees, the following data are obtained :

Complete sibships examined ophthalmoscopically.

Unaffected*			Affected		
M.	F.	P.	M.	F.	P.
5	5	10	13	11	24

* Excluding 3 women and two men under the age of 40.

Here there is no marked difference in sex distribution, but the discrepancy between the theoretical expectation as to frequency and the actual distribution is, however, wider, there being 24 affected individuals against 10 unaffected, a statistically significant difference. These ratios may, however, be loaded by the more ready submission to full examination by such sibships as are heavily affected. Until further data are available it would, therefore, seem best to assume a simple autosomal dominant mode of inheritance.

4. *Relationship to other affections.*

(*a*) *Doyne's Choroiditis.* The wide range of ophthalmoscopic appearances and extensive changes in their aspect in the affection recorded here has some features in common with the cases described by Doyne as "family choroiditis," or honeycomb choroiditis. In the families described by Doyne, and followed up by Tree (1937), the affection is also dominant and develops at about the age of 40 years. The characteristic appearance seems to be massive formation of white dots in the disc-macular area with only slight pigment proliferation. In some cases the choroidal vessels become exposed and possibly sclerosed, and haemorrhages may be seen during the course of the affection. But oedema and haemorrhages do not appear to be present during the early stages and extension peripherally does not appear to have been observed; in fact the process seems to be circumscribed by a circinate-like reaction, so that even in advanced cases the peripheral field is apparently not

involved. Histologically Doyne's choroiditis would appear to be a nodular hyaline degeneration of the pigment epithelium of the retina (Collins, 1913).

The final summary that Doyne gave of his cases would suggest that "white spots" and a strict localisation to the central area were the significant features. In his own words: "The condition may be summarised thus: It first appears in early adult life, but much more commonly later. It may either affect the disc neighbourhood, the macula neighbourhood, or the disc macula area. It consists of circular patches of exudation; these increase during the middle age, and at least, set up some irritation and pigmentary disturbance, for, though pigment is not always present, in some cases there is a good deal to be seen. During this stage the sight, though affected, is not grossly interfered with. In old age the condition passes into atrophy, with a corresponding degree of failure of sight."

It cannot, however, be excluded that the cases recorded as Doyne's choroiditis are actually examples of the affection reported here, and that in Doyne's cases (as in the first reports on the Kempster family and the Cranston sibship) a particular aspect has been stressed rather than the full picture. If the patterned reaction is indeed a constant feature in Doyne's choroiditis (and this would not appear to be the case) and if moreover Doyne's choroiditis does develop without preceding oedema at the macula, and in its later stages remains limited to the central areas (and the evidence on this is not conclusive) the affection described by Doyne would have to be regarded as a macular dystrophy of the "exudative type." It is, however, just as likely that the cases recorded by Doyne are instances of the affection described here, in which both the early and the late stages were not studied. The presence of patterned exudates in many of our patients is suggestive. The bare statement made by Doyne (1910) that he had had "two cases about eighty years of age, and they were almost blind" is likewise suggestive, as is also the remark that "the changes were different then, because the distinctive spots disappeared and the whole area [? central area or the whole of the fundus] became homogeneous and atrophic." It would appear that cases similar to those described by Doyne have been observed in the Leventino valley in Switzerland by Franceschetti (1948), whose brief note speaks of the presence of large hyaline bodies in a pre-senile macular degeneration with apparently irregular dominance. Until there is a fuller account of Doyne's choroiditis than is yet available, as also a histological study on the affection described here, the identity or otherwise of the two conditions must be left an open question.

(b) Retinitis punctata albescens and allied conditions.

Retinitis punctata albescens is an ill-defined entity. Even when the cases designated by Lauber (1910) as fundus albi punctatus are eliminated there is still left a rather heterogeneous mass. The group isolated by Lauber differs from retinitis punctata albescens in its congenital, non-progressive course, and in the fact that neither the disc nor vessels are involved; night blindness would, however, appear to be a constant feature. The stress laid by Doyne on "white spots" in his cases, the appearances depicted in Figs. 17 *a* and *b*, to a lesser extent in Figs. 6, 11 and 14, and to a slighter extent still in Figs. 1*a*, 2 *a* and *b*, 3, 18*a*, 24 *a* and *b*, 22 and 19*a*, raise the difficult question of the diagnostic significance of these "white spots." There is obviously no relationship between the condition recorded here and retinitis pigmentosa, even if the conception of retinitis pigmentosa is stretched to include "atypical" cases. The general absence of night blindness, the full peripheral fields almost until the end, the normal discs, and normal retinal vessels are quite conclusive. It is not improbable that the difficulty with "white spots" and "colloid" bodies and Drusen bodies arises from the fact that these are merely part of a wider picture, and the attempt to isolate clinical entities around these appearances has failed because of too narrow an approach. It may well prove that in a whole variety of affections the pigment epithelium reacts by the formation of non-pigmented hyaline excrescences; alternatively this reaction may be the basis of a wide range of ophthalmoscopic appearances.

(c) Other ill-defined entities.

The literature contains the following case reports of genetic fundus lesions that had become manifest at about the age of 40 years.

(1) Hutchinson (1875). Two sisters with central fundus lesions coming on at about the age of 57 and 48 years respectively.

(2) Leber (1916). A brother and two sisters with a central lesion setting in at the age of 50 years in the case of the brother, and at about 45 years in the sisters.

(3) Blue (1919). A macular lesion in a man affected at the age of 35 years, and a similar lesion in his daughter at the age of 12 years.

(4) Behr (1920). Two brothers, aged 43 and 53 years respectively, whose mother was probably also affected at the age of 50 years. These two brothers appeared to show a central lesion only.

(5) Clausen (1921). A man with a central lesion which developed at 41 years. Similar central lesions were found in three of his six children. They were 27, 19 and 15 years of age and their lesions had developed at 23, 10 and 13 years respectively.

(6) Cavara (1924). A macular lesion in three sibs; in two of them it developed at the age of 30 years and in the third at 40 years. In the youngest member the lesion was distinctly central; in the eldest member it had extended to engulf the whole of the disc-macular area.

(7) Mazzi (1934). A man who became affected with a central lesion at the age of 44 years had a son who showed a similar lesion at the age of 22 years.

Dominant inheritance is suggested by the cases recorded by Blue, by Clausen, and by Mazzi, but the age of onset in the second generation in each case would seem to exclude them from any affinity to the condition recorded here; moreover the lesion is recorded as central in position. The cases that might fit in best are those recorded by Hutchinson, Cavara, Leber, and Behr. Only in Behr's cases is there any suggestion of dominance; in the other three cases there is no information on either consanguinity, or of the affection being present in an earlier generation; and in none of these four cases is there any record on the evolution of the lesion.

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SUMMARY.

1. A description is given of five families which show an abiotrophic fundus lesion possessing the following features:

(*a*) The affection is dominant.

(*b*) It becomes manifest at about the age of 40 years.

(*c*) It begins as a central lesion showing oedema, haemorrhage, and exudates, thus closely simulating a retinitis. In the course of years there is atrophy with pigmentation of the central area and extension peripherally. The choroidal vessels become exposed and show some sclerosis. Ultimately—generally within 35 years—the whole of the fundus becomes involved; the choroidal vessels disappear and the terminal picture is one of extensive choroidal atrophy with pigmentation.

(*d*) There is no night-blindness antecedent to the development of fundus lesions or during the evolution of the affection.

2. This affection is a clear-cut entity, with a prognosis graver than that of a macular dystrophy, for which the earlier stages may be mistaken.

3. The course of the affection would suggest that the lesion is primarily choroidal.

4. Two of the five families recorded here have previously been reported mistakenly as examples of macular dystrophy with heavy pigmentary reaction and of central and peripapillary choroidal sclerosis. The polymorphism of an evolutionary affection presents many diagnostic difficulties, and the mistaken diagnoses in these two earlier records is illustrative of these difficulties.

5. The classical teaching that abiotrophic fundus lesions are recognisable as such ophthalmoscopically owing to their mottled or atrophic appearance, their sharply defined contours and the symmetry in the two eyes, is valid only for extreme cases. It may indeed be doubted whether there are any ophthalmoscopic features in lesions of environmental origin that cannot be found in abiotrophic affections.

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APPENDICES.

1. *The Randall Family.*

GENERATION I.

(1) Mrs. John Randall, née Ellard. According to two of her grandchildren (III, 12 and III, 16), Mrs. Randall died at about the age of 40 years and was not known to be affected. Both state, however, that a brother who survived to old age was affected. The two other surviving grandchildren (III, 3 and III, 4) both agree with their cousins that their grandfather was not affected. There was no consanguinity.

GENERATION II.

(1) Mary Ann Randall. Died aged 85 years. She had good sight and was unmarried. (2) William. Unmarried. Died aged 79 years. Had good sight.

(3) George Randall. His grandson, George Randall (IV, 2), reports that at about the age of 40 years he developed "centre blindness." He lived till the age of 72 years and "could see sideways." Used to get about the village comfortably. Concerning this patient, Mr. E. H. Harries-Jones writes: "I saw him about 40 years ago in a doctor's surgery with very poor light and found both retinae covered with pigmentary degeneration and central vision practically nil." Had six children (III, 1-6). (4) Richard Randall. Stated to have been affected. According to his daughter, Mabel (III, 12), his "central sight" went at the age of 40 years. Had six children (III, 7-12). (5) Sarah married Butt. Died at 65 years. Reported by her daughter, Amy (III, 16), to have become affected at 48 or 49 years. Her "central sight went." She died aged 65 years and was "four-fifths" blind. Had four children (III, 13-16). (6) Kate married Carr. Died aged 92 years. Her sight was "perfect" according to her niece, Amy (III, 16). Was the mother of two children (III, 17-18). (*a*) A seventh child, John, died as a baby. His position in the family cannot be definitely determined, nor the position of (*b*) a twin that died in early infancy

No member of this generation is alive to-day.

GENERATION III.

(1-6) The children of George Randall (II, 3). (1) John Randall died aged 67 years from renal failure after a prostate operation. He had retired from business as a corn merchant at the age of 52 years because of his eyesight, having developed "centre blindness" at about the age of 40 years. According to his daughter, Mary (IV, 1), he, like his father, could see to get about in the country and to look after his garden and outdoor work. Towards the end of his life his sight rapidly became worse. Mr. Harries-Jones saw him during the 1914-18 war and found "a central haemorrhage in one eye followed in about two years by the same condition in the other." Had two children (IV, 1 and 2). (2) George Randall was the editor of a local newspaper. According to his nephew, George (IV, 2), his sight became affected at about 45 years, but he carried on with his work until about 62 years. He died aged 64 years, after a prostate operation. He suffered from "centre blindness" and used telescopic glasses; his staff are said not to have realised that their chief could not read. His brother, Alfred (III, 6), reported that he underwent an extensive "mercury cure" which nearly killed him but produced no improvement in the sight. This patient was known to Mr. Harries-Jones as suffering from the same affections as the members of the family under his own care. He was unmarried. (3) Elizabeth married Clark. A frail old lady, aged 75 years, whose fundi show widespread lesions (Fig. 5). Her eyesight failed at the age of 40 years. She and her sister, Mrs. Thornton (III, 4), are known in the family as the most severely affected members. Is the mother of three children (IV, 3-5). (4) Annie married Thornton, is 71 years old. Very severely affected, possessing doubtful perception of light. Had a trephine operation on each eye at the age of 51 years by the late Mr. Nesfield, presumably not for glaucoma but for the relief of failure of sight which began at about the age of 40 years. Has two children (IV, 6 and 7). (5) William Randall, aged 70 years. Reputed to be normal and found so on examination. Has two children (IV, 8 and 9) and three grandchildren (V, 2-4), all reported to be normal and found so on examination. (6) Alfred Randall. Died from lymphatic leukaemia at the age of 57 years at the Westminster Hospital in 1938. Seen by one of us (A. S.) in 1937. His vision then was hand movements in each eye, and a diagnosis of central choroidal atrophy was made and the fundi were drawn. He gave a history of sight having failed progressively from the age of 43 years, but he could still find his way about London. He stated that his father had been likewise affected, and that only one of his five sibs had escaped the "family curse." It proved impossible at the time to follow this family up as the patient was unco-operative. He was unmarried. Whilst at the Westminster Hospital he was seen by the late Mr. A. D. Griffith, who reported that there were gross changes in the fundi "not at all connected, I should say, with the leukaemia." He regarded it as "a severe choroido-retinal atrophy such as follows luetic choroiditis." The blood Wassermann and Kahn were negative. This patient stated to one of us that he would not have any

treatment as he was sure to be "poisoned with mercury as his brother, George, had been."

(7-12) The children of Richard Randall (II, 4). (7) Rosa Randall. Unmarried. "Died blind" at about the age of 70 years, according to her sister, Mabel (III, 12). Trouble began at about the age of 40 years and progressed steadily. (8) Laura married Wrigley. Is alive and is 76 years old. Her sight is reputed to be normal, and her five children (IV, 10-14) are also reputed to be normal. (9) John Randall. Died at the age of 57 years of cancer. His sight had been "slightly affected" from "centre blindness." There was one son (IV, 15). (10) Gertrude married Cameron. Died at the age of 58 years. Is reputed to have been normal. Her three children (IV, 16-18) are also reputed to be normal. (11) Richard died at the age of 62 years. Reputed to have been normal, as are his five children (IV, 19-23). (12) Mabel married Pritchard. Is 67 years old. Reputed to be affected and found so on examination (Figs. *2a* and *2b*). Her trouble started at the age of 40 years. Has one son, John (IV, 24), who is affected.

(13-16) The children of Sarah Butt (II, 5). (13) Kate married Flatt. Died at the age of 30 years, reputed to have been normal, as are her two children (IV, 25 and 26). (14) Florence married O'Hara. Died aged 72 years. Lost "central sight" at 42 years, but could always see to get about. There were no children. (15) Lucy Ellen married Barrett. Is alive, aged 70 years, and is reputed to be normal, as are her two children (IV, 27 and 28). (16) Amy married Martin. Lost "central vision" at 41 years. Is now 68 years. Was not much handicapped till aged 60 years. Her fundi show a central lesion (Fig. 3). Has two children (IV, 29 and 30).

(17 and 18) Tom and Nellie, the children of Kate Carr (II, 6). This branch of the family is reported as normal and has not been followed up. Tom is 69 years, Nellie is 61 years.

GENERATION IV.

(1 and 2) Mary and George, the children of III, 1. Mary is the starting point of this study. Her fundi are depicted in Figs. *1a*, *1b* and *1c*. A fuller account is given in the text. George, aged 27 years, reputed to be normal and found so on examination.

(3-5) Noel, Winifred and Muriel Clark, the children of III, 3. Noel was killed in the World War I, aged 22 years. Winifred, now aged 51 years, married Johnson. Reputed to be normal and found so on examination. Muriel, aged 47 years, married Burton. Reputed to be normal and found so on examination.

(6 and 7) Mary and Phillip Thornton, aged 33 and 31 years, the children of III, 4. Reputed to be normal and found so on examination.

(8 and 9) Dora and Margaret, the children of III, 5. Dora, aged 41 years, married Fleming. Reputed to be normal and found so on examination. Margaret Randall, aged 35 years, reputed to be normal and found so on examination. Is unmarried.

(10-14) Children of Laura Wrigley (III, 8). (10) died aged 30 years, unmarried. (11-14) Reputed to be normal. Have not been examined.

(15) Eric Randall, the son of III, 9. He is aged 46 years and is reputed to be normal. Not seen.

(16-18) The children of Gertrude Cameron (III, 10). (16) Died aged 10 weeks. (17 and 18) are 38 and 36 years of age respectively. Not seen.

(19-23) The children of Richard Randall (III, 11). (19) Died in childhood. (20) Is aged 40 years. His three younger sibs are younger by two years progressively. All reputed to be normal. Not seen.

(24) John Pritchard, the son of III, 12. When seen at the age of 43 years he was reputed to be normal and found so on examination. Six months later the right eye failed. He is discussed fully in the text.

(25 and 26) The children of III, 13. Lilian married England. Is aged 50 years. Has two children (V, 15 and 16). Winifred, aged 45 years, married Eldon. Has one daughter (V, 17). All reputed to be normal. Not seen.

(27 and 28) Ivor and Myfanwy, the children of Lucy Barrett (III, 15), aged 44 and 36 years. Reputed to be normal. Not seen.

(29 and 30) Joan and Albert, the children of Amy Martin (III, 16), aged 31 and 28 years respectively. Both reputed to be normal. Joan was found so on examination.

(31 and 32) The children of Tom Carr (III, 17), Freddie and Joyce. Reputed to be normal. Not seen.

GENERATION V.

None of this generation is beyond adolescent age and none is reported affected.

(1) David Johnson, the son of IV, 4.

(2, 3 and 4) A son, Robert, and two daughters of Dora Fleming (IV, 8), aged 8, 6 and 3 years respectively.

(5-8) The grandchildren of Laura Wrigley (III, 8), herself unaffected.

(9-10) Sheila and Barbara Randall, the children of IV, 15.

(11) Grandchild of III, 10.

(12 and 13) The grandchildren of Richard Randall (III, 11), himself reputed to be unaffected.

(14) The son of John Pritchard (IV, 24, himself affected), aged 6 months.

(15 and 16) John and Jean England, aged 25 and 21 years respectively.

(17) Daughter of Winifred Eldon (IV, 26), aged 16 years.

(18 and 19) Jean and John, the grandchildren of III, 17, himself reputed normal.

2. *The Carver Family.*

GENERATION I.

(1) Mr. Carver. The family ascribes the eye defect as originating with Mr. Carver, and the condition is known in the family as the "Carver eye."

GENERATION II.

(1) Dinah Carver married Hepburn. (2) William Carver. (3) Edward Carver. (4) Jane Carver, unmarried, died elderly. (5) Dan Carver. (6) Anthony Carver. (7) Dryden Carver. (8) Mary married Murray. Of this generation all but Edward, Jane and Anthony are said to have been affected.

GENERATION III.

(1-5) The children of Mrs. Dinah Carver-Hepburn (II, 1): Dan Hepburn (1), died at about 54 years of age, reputed to be unaffected. Catherine (2) married Wilson, died under 40 years, reputed unaffected. Anthony Hepburn (3), age 75 years. Lizzie (4), died under 40 years, reputed unaffected, and Dryden Hepburn (5), aged 65 years. Anthony reputed to be affected and found so on examination. Dryden is reputed to be affected.

(6-10) The children of Dan Carver (II, 5): John Carver (6), died at 78 years, a daughter (7) died at 16 years, Ellen (8) married Lace; is 72 years of age, reputed to be affected and found so on examination, Emma (9) died in infancy, and Isabel (10) married Wright; examined and found normal; died at 62 years.

(11-16) The children of Anthony Carver (II, 6): Annie (11), Jane (12), Mary (13), John (14), William (15) and Dryden Carver (16). Annie, the eldest, married Duncan Kirkpatrick; she is reputed to be affected and was found so on examination; is now 65 years old. Jane married Dixon; she is now dead. Mary is in America; John Carver died under 40 years, William and Dryden are over 40 years, alive and in America.

(17-24) The children of Mary Carver Murray (II, 8): Ann (17), Mary (18), John Batey (19), Jane (20), Dryden (21), Maggie (22), Jessie (23), and another sister (24). The eldest, Ann, married Tyson, died at about the age of 80 years; she was reputed to be unaffected. Mary was unmarried and was reputed to be affected. John Batey was reputed not to be affected but was found affected on examination; he is now 78 years old. Jane died under 40 years. Dryden died at the age of 73 years; was reputed to be affected and was found so when examined some years ago. Maggie, married Wallace; was reputed to be affected; she is dead. Jessie,

aged 71 years, is reputed to be affected and was found so on examination; married to McLean. The youngest daughter is over 40 years; she is married to Cape.

GENERATION IV.

(1-3) The children of Dan Hepburn (III, 1): Mary Hepburn (1), aged 56 years, and Mrs. Spedding (2), aged 46 years, were examined and found normal. Archie Hepburn (3), aged 42 years, lives in Rochdale; not examined.

(4-7) The children of Catherine (Hepburn) Wilson (III, 2): Archie Wilson (4), died aged more than 40 years; Dinah (5) married Dawson, is now 69 years old and was found normal on examination; Harriet (6) married Hodgson; Reuben Wilson (7) is now about 65 years; examined and found normal.

(8-16) The children of Anthony Hepburn (III, 3): Nellie (8), aged 52 years, married Bedford; reputed and found to be affected. Archie Hepburn (9), aged 50 years, reputed and found to be affected. John Hepburn (10), aged 47 years, reputed and found to be affected. (11) Margaret, aged 46, patient No. 5 in the text. Emma (12) married Rudd, aged 45 years; found normal on examination. Jim Hepburn (13), aged 44 years, reputed and found to be affected. Annie Hepburn (14), aged 42 years; found normal. Dryden (15), aged 40 years, found normal. Mary (16), aged 37 years, found normal.

(17-19) The children of Dryden Hepburn (III, 5): Frank (17) is 38 years old, Douglas (18) is 33 years, and Graham (19) is 30 years.

(20-29) The children of Ellen Lace (III, 8): Sarah (20), married Hayes, is now 54 years old; reputed and found to be affected. Martha Lace (21), aged 52 years; found normal. Margaret (22), aged 48 years, married Prickett; reputed to be affected. Ellen (23), aged 45 years, married Jim Murray (IV, 38, himself affected), found normal on examination. Fred Lace (24), aged 44 years, Isabel Lace (25), aged 42 years, found normal. John Daniel Lace (26), aged 40 years, found normal. Dorothy (27), aged 38 years, married Wilson. Mary Irving (28), married Wilson, aged 37, found normal. Gordon Lace (29), aged 33 years, found normal.

(30) A son of Isabel Wright (III, 10). Died in the early twenties from tuberculosis.

(31 and 32) The children of Annie Kirkpatrick (III, 11): Leo (31) died aged 39 years. His younger sister, Nancy (32), is alive under 40 years.

(33 and 34) The children of Jane Dixon (III, 12): William (33) is 25 years old. Harriet (34) is a younger sister.

(35) A son of John Carver, aged under 40 years.

(36) John Ernest Murray, a son of Ann Tyson (III, 17), is reputed to be and found affected. He is 59 years of age.

(37-40) The children of Dryden Murray (III, 21): Mary (37), aged 54 years, married Dixon; found normal. Jim Dryden Murray (38), aged 50 years, reputed and found to be affected. He is married to Ellen Lace, now aged 45 years (IV, 23); herself normal. Emma (39), aged 43 years, married Parker; reputed normal. William Murray (40), aged 39 years when killed in the William Pit Disaster in 1947; was known to be unaffected.

(41-48) Eight daughters of Maggie Wallace (III, 22, herself reputed to be affected). Reputed that one daughter living in Scotland is affected. This branch of the family could not be followed up.

(49-54) The children of Mrs. Cape (III, 24): the eldest daughter (49), aged 64 years, married Bland and lives in Newcastle. James Cape (50) is 61 years old. William Cape (51), Harry Cape (52), and two younger sisters (53 and 54) are the other children. All are over 40 years of age, but none could be examined. They are reputed not to be affected.

GENERATIONS V.

In this generation there are no individuals who have as yet reached the age of 40 years.

(1 and 2) The two daughters of (IV, 2), aged 26 and 25 years respectively.

(3) A son of Archie Hepburn (IV, 3), aged 23 years.

(4 and 5) The two sons of Nellie Bedford (IV, 8) herself affected. The eldest, Anthony Bedford, died at the age of 24 years. His brother, Stephen Bedford, is aged 23 years.

(6-9) The children of Archie Hepburn (IV, 9) himself affected: Dennis (6), Jim (7), Eileen (8), Neil (9) are aged 25, 23, 15, and 7 years respectively.

(10-11) The children of John Hepburn (IV, 10) himself affected: Kathleen (10), Mary (11) are aged 19 and 10 years respectively.

(12-15) The children of Emma Rudd (IV, 12): Mary (12), Jean (13), Anthony (14), Howard (15), are aged 19, 13 and 10 years respectively.

(16) Ian, son of Jim Hepburn (IV, 13), himself affected, is aged 17 years.

(17-19) The children of Sarah Hayes (IV, 20) herself affected: Joseph (17) died at 26 years, John (18) is 26 years old, and Phyllis (18) is 14 years.

(20-26) The children of Margaret Prickett (IV, 22) herself reputed affected: Vera, Josephine, Brian, Mary, John, Ellen, and Fred, aged 26, 24, 23, 21, 19, 17, and 14 years respectively.

(27) Marjorie Lindsay Murray, aged 23 years, the daughter of Ellen Lace (IV, 23) and Jim Murray (IV, 38), himself affected, was found normal on examination.

(28) Mary Lace, the young daughter of IV, 24, aged 16 years.

(29) John Lace, son of IV, 26, is 14 years old.

(30) The son of Dorothy Wilson (IV, 27) is 11 years old.

(31) The son of John Ernest Murray (IV, 36), himself affected, is 33 years old.

(32 and 33) Nora, aged 27 years, and Raymond Dixon, aged 26 years, children of IV, 37.

(34-36) Yvonne, Margaret and Alan Murray, aged 5, 4 and 2 respectively, grandchildren of III. 21, himself affected.

3. *The Ewbank Family.*

GENERATION I.

Mr. Ewbank died in his fifties; is not known to have had any defect of vision. He married twice. All that is known of the first marriage is that there were children.

GENERATION II.

The information concerns the seven children of the second marriage.

(1) Sarah Ewbank, died aged 67 years, unmarried. Reputed to have been unaffected. (2) Cornelius Ewbank, died at 55 years, unmarried. Reputed to have been unaffected. (3) Josephine, married Adamson. Sight became affected in the early forties; was "practically blind" when she died at 60 years. (4) Susie, died at about the age of 20 years. (5) Rosa, married Steele. Sight became affected at about 35 years. Died "practically blind" at the age of 62 years. (6) Florence, died at 74 years. Reputed normal. No issue. (7) Richard Ewbank. Sight became affected at 43 years. He was seen by the late Mr. R. P. Brooks, who found "maculitis." The patient "was soon unable to read, but always retained some sight (*e.g.*, could play cards, do some gardening and go about unaccompanied)." (Information given by his son Maurice, III, 10.) Died at 74 years. He was the father of the patients recorded here.

GENERATIONS III.

(1-4) The children of Josephine Adamson (II, 3). (1) Bert Adamson, died unmarried at 32 years. (2) Florence, aged 67, married Patchett. "Had severe haemorrhage in the eyes at 48 years; has peripheral vision only (cannot read or sew, but can play cards and gets about)." Has one son aged 32 years. (3) Isabelle, aged 61 years, married Jagger; no children. "Present condition similar to that of her sister Florence." Sight is said to have deteriorated at 58, but when seen by Sir Stewart Duke-Elder in 1947, when she was aged 60 years, he found advanced central choroidal atrophy in both eyes, more marked in the right than in the left. (4) Marjory, aged 54 years, married White; "Sight has been deteriorating for the past four years." Has one son.

(5-8) The children of Rosa Steele (II, 5), herself reputed affected. (5) Mary, now aged 55 years, married Cockayne. Sight has been bad for 20 years. Has four children. (6) Constance, aged 52 years. Reputed unaffected. Has one daughter.

(7) Wallace Steele, aged 50 years. Reputed unaffected. (8) Rosa, aged 46 years, married Grahame. Has two sons.

(9-12) The children of Richard Ewbank (II, 7, himself affected) by his first wife, who died aged 43 years and was unaffected. (9) Kenneth Ewbank, aged 54 years, is mentally defective, but is said to have no eye trouble. (10) Maurice Ewbank, aged 48 years, examined and found to be affected. (11) Colin Ewbank, aged 46 years, died from neoplasm of the kidney. Known to have been affected since the age of 36 years. (12) Mary, aged 43 years, married Waterer. Examined and found affected.

(13 and 14) The children of Richard Ewbank (II, 7) by his second wife. (13) Kathleen, aged 40 years, married Hughes. Examined and found affected. (14) Nora, aged 38, married Holland. Examined and found unaffected.

GENERATION IV.

(1) Bert, the son of Florence Patchett (III, 2); aged 32 years.
(2) The son of Marjory White (III, 4): Tony, aged 25 years.
(3-6) The children of Mary Cockayne (III, 5), herself reputed affected; Constance, aged 26 years, married Marshal, has one daughter; Nora, aged 23 years, married Dyer; twin brother and sister aged 17 years.
(7) Cynthia Stevenson, aged 14 years, daughter of III, 6.
(8 and 9) Gerald and Maurice, sons of III, 8, aged 21 and 19 years respectively.
(10) Denis, aged 29 years, the son of Kenneth Ewbank (III, 9).
(11-13) The sons of Maurice Ewbank (III, 10), himself affected. (11) Anthony, died aged 20 years. (12) Patrick, aged 17 years, and (13) David, aged 13 years.
(14-15) The children of Mary Waterer (III, 12), herself affected. (14) John Waterer, aged 9 years, and (15) Patricia Waterer, aged 4 years.
(16-17) The children of Kathleen Hughes (III, 13), herself affected. (16) Robin, aged 8 years, and (17) Wendy, aged 4 years.
(18-19) The two daughters of Nora Holland (III, 14). Elizabeth, aged 4 years, and Carolyn, aged 8 months.

GENERATION V.

(1) The baby daughter of (IV, 3).
(2) The baby daughter of Denis Ewbank (IV, 10).

4. *The Kempster Family.*

GENERATION I.

The grandfather of the observed patients is reported to have been blind. He is also reported to have had a blind brother.

GENERATION II.

The grandfather's brother is reported to have had an affected daughter. As for the grandfather's children there were 8, the order of whom is not known. Three out of five brothers are reputed to have been affected and one out of three sisters.

GENERATION III.

It is reported that two cousins of the present sibship are affected, the son of a paternal uncle, and the daughter of a paternal aunt. The sibship itself (III, 1-10) has been described in the text.

GENERATION IV.

(1) RUTH HALL, the daughter of Alice Hall (III, 1), herself affected, aged 30 years, unmarried; examined and found normal.
(2-5) The children of Caroline Poulton (III, 2), herself affected. (2) Ivy, married Collins, aged 32 years; reputed normal. (3) Gladys Poulton, unmarried, aged 31 years, seen and found normal. (4) Frances, married Cook, aged 29 years; reputed normal. (5) A son: premature stillbirth.
(6-9) The children of William Kempster (III, 4), himself affected. The eldest, a son, died at 21 years, was reputed normal. (7-8) Two girls died in infancy at

four weeks and six months. Joan Kempster, aged 24 years, unmarried, reputed normal.

(10-14) The children of Ann Redding (III, 5), herself affected. (10) Winifred, aged 35, reputed normal. (11) William Redding, aged 33 years, reputed normal. (12) Ann, married Puddephat, aged 31 years; reputed normal. (13) Dorothy, married Blunt, aged 28 years, reputed normal. (14) Percival Redding, aged 26 years, reputed normal.

(15-17) The children of Rose Graves (III, 6), herself affected. All in Canada. Rosemary Graves, aged 29 years, is reputed to be mentally defective; unmarried. Doris Graves, aged 27 years, reputed normal, unmarried. Robert Graves, aged 21 years, reputed normal; was seen in 1939, at the age of 12 years, and was then found normal.

(18) Thomas Wood, the son of Eliza Wood (III, 7), aged 25 years; reputed normal.

(19) Sidney Kempster, son of Joseph Kempster (III, 8), himself affected, aged 28 years, married, no children; reputed normal.

(20-23) The children of Arthur Kempster (III, 9), himself affected. (20) Herbert, aged 26 years. (21) Fred, aged 24 years. (22) Robert, aged 17 years. (23) John, aged 9 years. All reputed to be normal.

(24 and 25) The children of Robert Kempster (III, 10), Gwen, aged 18 years, and Margaret, aged 14 years, reputed to be normal.

GENERATION V.

(1 and 2) Ronald and Josephine Collins, aged 2 and 1 years, children of IV, 2.

(3) Michael Cook, aged 1 year, son of IV, 4.

(4-6) (4) Brenda, aged 8 years, Anthony, aged 5 years, Nita, aged 2 years, children of William Kempster (IV, 11).

(7-8) Harold and Sandra Puddephat, aged 8 and 6 years respectively, children of IV, 12.

(9) Stephen Blunt, aged 4 months, son of IV, 13.

(10) Stewart Redding, aged 14 months, son of IV, 14.

(11) Margaret Kempster, aged 12 months, daughter of IV, 20.

A THEORETICAL PLAN OF A METHOD FOR REMOVING NON-FERRO-MAGNETIC METALLIC INTRA-OCULAR FOREIGN BODIES BY MEANS OF ELECTRO-MAGNETIC FORCES.*

BY

P. M. ENDT *and* J. TEN DOESSCHATE

UTRECHT

THE removing of non-ferro-magnetic metallic intra-ocular foreign bodies (like copper, non-magnetic steel, etc.), always offers many difficulties to the ophthalmologist. For removing ferro-magnetic foreign bodies we have at our disposal very satisfactory methods which are all based on the principle of exerting electro-magnetic forces on the foreign body. Theoretically, however, it is possible

* A paper on this subject was read by the authors at the 112th meeting of the *Netherl. Ophthal. Soc.* on June 7, 1947. This paper did not contain the necessary physical foundations.

to exert electro-magnetic forces also on non-ferro-magnetic bodies. In this paper we propose to give a theoretical development of a method which will allow the removing of such foreign bodies, provided a high frequency electro-magnetic field of sufficient strength can be produced.

First, the principles of the new method will be given qualitatively.

In the metallic particle in question an alternating induction current is generated by a high frequency magnetic field. For simplicity let us assume the particle to be a little ring in a plane at right angles with the direction of the magnetic field. Now there exists a well-known analogy of a ring current with a magnetic dipole. On a magnetic dipole a force is exerted by an inhomogeneous magnetic field. Analogously also the ring undergoes a force by the magnetic field, provided the alternating current in the ring is in phase with the alternating magnetic field. The latter is true when the frequency is so high, that the inductance of the ring is large compared with its resistance.

Now we will follow this argument quantitatively. Here, however, we will assume the particle to be a little sphere (radius R).

By an alternating magnetic field $H(t)$ a magnetic dipole is induced in the particle with dipole strength [1]:

$$\vec{p}(t) = -\tfrac{1}{2} R^3 \vec{H}(t) \ \ (e.s.u.) \qquad \dots \qquad \dots \qquad (1)$$

This relation is subject to two restrictions. First the frequency ν must be so low, that the wavelength related with it: $\lambda = c/\nu$ (c=velocity of light) is large compared with the radius of the particle. This restriction is not at all severe. On the other hand the penetrating depth d of the skin effect must be small compared with the radius:

$$d = \frac{c}{2\pi\sqrt{\nu\sigma}} \ll R . \qquad \dots \qquad \dots \qquad (2)$$

Here σ is the electrical conductivity of the particle in *e.s.u.*

The force exerted on the particle will now be given by:

$$\vec{F}(t) = (\vec{p}(t) \ grad) \ \vec{H}(t) = -\tfrac{1}{4} R^3 \ grad \ (H^2(t)) .$$

This force is still dependent on time. The mean force is given by:

$$\overline{\vec{F}} = -\tfrac{1}{4} R^3 \ grad \ (H_{\sim}^2) , \qquad \dots \qquad \dots \qquad (3)$$

where $H_{\sim}$ is the root mean square value of the magnetic field $H(t)$. Preliminary experiments done by one of us in the Physical Laboratory of the University of Utrecht with a small high-frequency generator showed that this force has the expected order of magnitude.

More important than the force itself is the ratio of the electromagnetic force to the force of gravity (G) exerted on the particle:

$$F/G = \frac{1/4\ R^3\, grad\ (H_\sim^2)}{4/3\ \pi R^3 \rho g} = \frac{3}{8\pi}\ \frac{H_\sim\, grad\, H_\sim}{\rho g}, \qquad \ldots \qquad (4)$$

where ρ is the density of the particle and g the acceleration of gravity. We see that this ratio is independent of the radius of the particle.

Let us compare equation (3) with the force exerted on an iron sphere (permeability μ) with the same radius R by a constant magnetic field. This force is given by:

$$\vec{F} = \frac{1}{2}\ \frac{\mu - 1}{\mu + 2}\ R^3\, grad\ (H^2)\,. \qquad \ldots \qquad \ldots \qquad (5)$$

With $\mu \gg 1$ we have:

$$\vec{F} = \frac{1}{2}\ R^3\, grad\ (H^2)\,. \qquad \ldots \qquad \ldots \qquad (6)$$

Comparing (3) and (5) we note that the force on a copper particle in an alternating field is identical with that on a diamagnetic sphere ($\mu \ll 1$) in an equal constant field.

Comparing (3) and (6) we see that if $H_\sim = H$ there remain two differences:

1—The force on the copper sphere is one half of that exerted on the iron sphere. This is not serious.

2—The force in (3) has the minus sign. Whereas the iron particle is drawn into the coil producing the magnetic field, the copper particle is pushed out of it. This is rather a serious disadvantage. To extract particles out of the eye the coil must be held behind the head. The distance from the coil to the eye now being large, the alternating current in the coil must be very strong to produce a magnetic field of sufficient strength.

Another unwanted effect is the generation of heat in the particle by the induction current, given by [1]:

$$W = \frac{3}{4}\ R^2\ H_\sim^2\, c\ \sqrt{\nu/\sigma}\ erg/sec\,. \qquad \ldots \qquad \ldots \qquad (7)$$

The heat conductivity of the ocular fluids being A, the temperature excess of the particle becomes:

$$\theta = \frac{W}{4\pi RA} = \frac{3}{16\pi}\ \frac{RH_\sim^2 c\sqrt{\nu/\sigma}}{A} \qquad \ldots \qquad \ldots \qquad (8)$$

If the particle were to become too hot, albumen in the ocular fluids would coagulate around the particle.

The force of the particle being, between the limits given, independant of the frequency, it is clear that we will use a frequency as low

as possible in order not to heat the particle excessively. Let us choose the frequency so that the penetrating depth of the skin effect (see (2)) equals one half the radius of the particle:

$$d = \frac{c}{2\pi\sqrt{\nu\sigma}} = \tfrac{1}{2}R. \qquad \ldots \qquad \ldots \qquad (9)$$

The temperature excess now becomes independent of the radius:

$$\theta = \frac{3c^2}{16\,\pi^2\sigma\Lambda}\,H_{\sim}^{\,2}. \qquad \ldots \qquad \ldots \qquad (10)$$

As an example we will consider an aluminium particle ($\rho = 2{\cdot}7$, $\sigma = 3{\cdot}4 \times 10^{17}$ *e.s.u.*) of arbitrary radius. We take the heat conductivity of the ocular fluids as equal to that of pure water: $\Lambda = 6 \times 10^4$ erg/sec cm °C. If the magnetic field has an *r.m.s.* value of 300 Oerstedt and the gradient of the *r.m.s.* field is 100 Oerstedt/cm., then we have from (4) and (10) ($c = 3 \times 10^{10}$ cm/sec, $g = 981$ cm/sec^2):

$$F/G = 1.34 \text{ and: } \theta = 74\ °\text{C}.$$

The optimum frequency given by (9) becomes:

$$\nu = \frac{c^2}{\pi^2 R^2 \sigma}. \qquad \ldots \qquad \ldots \qquad \ldots \qquad (11)$$

For an aluminium particle with $R = 1$ mm. we have: $\lambda = 26$ kHz.

For copper particles the temperature excess is larger, if F/G is kept constant; the electrical conductivity is larger but the density is also larger.

It may be necessary to operate the magnetic field only during short time-intervals in order to keep down the temperature of the particle.

Summary

A theoretical development is given of a method which will allow the removal of non-ferro-magnetic metallic intra-ocular foreign bodies by means of a high-frequency electro-magnetic field, provided a field of sufficient intensity can be produced and the difficulties connected with heat generation can be overcome.

The authors wish to express their sincere thanks to Professor Dr. J. M. W. Milatz for his lively interest in this work.

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NOTES ON 221 INTRA-CAPSULAR CATARACT EXTRACTIONS PERFORMED IN THREE WEEKS AT KHAIRPUR IN 1947

BY

SIR HENRY HOLLAND *and* R. W. B. HOLLAND

INDIA

[DURING this three weeks in 1947 there were also 172 extra-capsular extractions and needling operations performed by my son, R. W. B. Holland, and myself.]

All the intracapsular extractions were done by the Smith method of expression and not extraction by any of the various forceps used, *e.g.*, Kalt, Elschnig, Arruga, Knapp, Sinclair, and Kirwan. I am perfectly aware that this method has been and is still adversely criticised. Its opponents affirm that the pressure required to rupture the zonule must be detrimental to the eye, and also that the loss of vitreous is much more frequent than in the extracapsular method or the forceps methods of extraction. Another objection brought forward is the supposedly frequent occurrence of detachment of the retina following cases in which there had been vitreous escape at the time of operation. Although our staff has performed over 30,000 intracapsular extractions since 1909, I have seen only 2 cases of detachment of the retina following the operation. We are always on the look out for this complication, and when any patient returns complaining of diminution or loss of vision we always examine the fundus carefully in the dark room.

I admit that for the beginner the Smith operation is much more difficult than either the extracapsular or the intracapsular extraction with forceps. We have had 138 visiting surgeons at our Shikarpur clinic, and I always impress on them that no one should attempt an intracapsular Smith operation until he has done at least 50 or more extracapsular extractions. Furthermore, the Smith operation should not be done if a surgeon does only about 5 or 6 cataract extractions a month. It is an operation in which it is necessary to preserve one's sense of touch by constant practice. Having had 38 years of experience I consider that as far as I am concerned the Smith operation is the best for extraction of ordinary senile cataracts, and is the least traumatic procedure to the eye of any method.

There are, however, very definite contra-indications to the Smith operation. They are: (a) Glaucomatous cataract. (b) Cataract with tension over 35 mm. mercury. (c) The big "ox eye,"

found in very plethoric individuals. In these there is a great tendency for the vitreous to be degenerate and liquid in character with consequent danger of loss. (d) Cataract in the young patient. I always do an extracapsular extraction if the patient's hair has not begun to grow grey. (e) Congenital cataracts. (f) Traumatic cataracts. (g) Complicated cataracts—with synechiae, etc. (h) All those cases in which a legitimate amount of pressure does not succeed in rupturing the zonule. Only practice will enable the operator to decide when he has exercised sufficient pressure. If the pressure is applied at the right point and directed in the right axis, only very little pressure is needed in the great majority of cases. The golden rule in this operation is to cease the pressure if the upper pole of the lens does not present in the wound at once. In such cases the operator should replace the speculum and perform an extracapsular operation. 90 per cent. of cases of vitreous escape are due to too prolonged and too great pressure. If the zonule is tough the skilled operator will realise this and be humble enough to desist. He should never make up his mind that in a certain case he is going to do a Smith operation come what may. If he does so, he will often regret his decision. By all means he may say that he will attempt a Smith extraction, but he should be prepared to abandon the attempt should the upper pole of the lens not present at once. I am often amazed at the ease with which the lens is dislocated. At times a mere touch is given on the lower pole of the lens and it " almost walks out to meet you."

My object in this article is to present in detail the results of the Smith operation in the 221 cases under review. I feel I must refer to the Barraquer suction grasp method of extraction since we have tried it in Shikarpur when some 200 cataracts were removed by this method. Our results, except for those done by Lt.-Col. Cruickshank, were not as good as those done by the Smith method, but I have seen Barraquer operating in his clinic at Barcelona, and in his hands the operation produces extremely good results.

The salient points of the Smith operation after the incision and iridectomy are as follows:—

The assistant must take complete control of both upper and lower lids. The upper lid is lifted forward by means of a blunt double hook retractor, the two limbs of which are about half an inch apart. The handle of the retractor is held between the assistant's thumb, index and middle fingers, while the ring and little fingers of the same hand are used for retracting the upper eyebrow, thus fully controlling the upper part of the orbicularis oculi. The lower lid is retracted by placing the thumb of the

other hand flat on the skin immediately below the eye and by drawing it down with the help of a sterile cotton wool swab. I have mentioned this in detail because the assistant's share in the operation is all-important. It must be remembered that the blunt hook retractor is used for lifting up the upper lid to gain access to the eye, and must not be used for pulling on the lid.

The operator now proceeds to dislocate and extract the lens. He takes the spatula in his left hand, placing the end at about 45 degrees on the sclera just below and to the left of the sclero-corneal junction between 4 and 5 o'clock. With his right hand the operator takes a blunt hook. Both hands should be supporting the patient's head, which will ensure greater steadiness and delicacy of movement on the part of the operator. The ball end of the hook is then applied and pressure exerted over the lower third of the cornea in a direction straight back towards the optic nerve, the spatula at this stage being kept quite stationary and used chiefly to steady the eyeball. If the upper pole of the lens does not appear at once in the wound, the ball end of the hook is made to pass slightly from side to side which movements generally succeed in dislocating the lens. Should legitimate pressure not succeed in dislocating the lens, the assistant releases his hold on the eyelids and the speculum is inserted and extraction is made by the extracapsular method. If the lens dislocates it should be followed up by the ball end of the hook, and the pressure on the spatula gradually reduced.

Points of interest in this series

1. *Anaesthesia.* The usual routine was 4 per cent. cocaine surface anaesthesia with facial nerve block. In addition to this, 13 cases were given a retro-bulbar injection of 1/2000 pantocaine-adrenalin. This produced a painless iridectomy, but did not seem to render the operation any easier.

General anaesthesia was given to 28 adults and to all children suffering from congenital cataract. This course was adopted in all cases where it was previously expected that the patient would have little or no self-control, and also when the lack of control was first demonstrated when the surgeon attempted to insert the speculum although local anaesthesia had been already well established. The figures for the respective types of anaesthesia were chloroform 17, pentothal 7, and intra-venous 1 per cent. avertin in saline 4. Many ophthalmic surgeons are afraid to administer chloroform for fear of vomiting and consequent expulsive haemorrhage. In my experience of several hundred such cases, I can only remember one instance of expulsive

haemorrhage occurring after chloroform anaesthesia, and I am quite certain that I have saved many eyes by giving a general anaesthetic, and thus saving the straining of a nervous patient. On looking back over an experience of many thousands of cataract extractions, I am convinced that if we have erred, it has been in not giving a general anaesthetic in a sufficient number of cases. If the patient is not "good," it is the surgeon's duty to see that he is rendered "good" by the administration of a general anaesthetic.

2. *Burst Capsule.* This occurred in 14 cases, in most of which the capsule was removed with iris forceps at the time of operation.

3. *Vitreous Loss.* This occurred in six cases. In one case akinesia was not complete, and the patient squeezed after the delivery of the lens. His loss was denoted by + +. In one case the loss was noted as +, and in the other four cases it was recorded as slight. In all except the case first described, the vision was ultimatedly good or very good. In four cases the vitreous was lost after delivery of the lens, and in two cases before it.

4. *Iridectomy.* There were 64 full iridectomies, 84 peripheral iridectomies, and 13 cases when no iridectomy was performed.

The iridectomy was always done before the lens extraction because the patients' powers of restraint after the delivery of the lens are obviously to a large extent exhausted and they are apt to become nervous and to squeeze. In thirteen cases no iridectomy was done, which was a safety measure, as the patient became nervous and refused to look down.

In five cases a full iridectomy was accidentally performed with the knife on making the incision, and in 2 cases a peripheral iridectomy. In all these cases the visual result was excellent.

There were 8 cases of prolapsed iris in the 84 cases of peripheral iridectomy, two in the 64 cases of complete iridectomy, and 5 in the 13 cases where there was no iridectomy performed. In this series no sclero-corneal or other suture was used, but a stitch in the upper lid is inserted before operation and attached with sticking plaster to the cheek afterwards to keep the lid down during the period of akinesia.

5. *Dressings.* The intracapsular cases are not opened until the 6th day after operation and the capsulotomies on the 3rd or 4th day. Any iris prolapse is excised or cauterised on the 9th or 10th day after operation.

6. *Selection of Cases.* If all our patients had presented themselves with uncomplicated senile cataracts, our percentage of intracapsular extractions would have been very much higher, and

our results much better. But a glance at the previous list of contra-indications to the Smith operation, coupled with the fact that we have to undertake a large number of very poor risk cases, such as those complicated by old cyclitis, iritis, trachoma, leucoma and glaucoma, will at once show why we were compelled to do so many more extracapsular extractions than we would have chosen. Also a number of cases were accepted for operation on the clear understanding that benefit might or might not result, and in any case the benefit would be only slight. However, on looking back over a period of 40 years' experience in operative ophthalmology, I find that the results of operating on apparently hopeless cases has often been better than I had dared to hope. If a patient after treatment was able to see hand movements, whereas previously he had only perception of light, it was well worth while for him to have come, since his condition was made definitely better. As an example, I remember a case of an old man, aged 85, on whom I operated a year ago. One eye had twice been injured, once by a crowbar when a very young man, and later on by the tip of a billiard cue. At the time of operation he had only perception of light. I operated, and ultimately he was not only able to find his way about quite comfortably, but could also distinguish large letters in a newspaper.

7. *Visual Results*. It is impossible to be dogmatic about these, since accurate end results in this country are impossible to obtain, because the majority of patients on whom we operate are not seen again after their stay of about 12 days in hospital until our subsequent visit to the eye camp a year later; and also because only about 5 per cent. of cases are literate, and even less than this proportion can afford an astigmatic lens where needed.

The majority leave with good vision as assessed by the rough test of counting fingers rapidly at 3 or 4 feet, increased to 20 or 30 feet with a +9 or +10 lens, and by comparing these results with those obtained by refracting and testing carefully the few literates we have, we are able to arrive at a fairly reliable estimate of the probable vision of the illiterates.

Commentary. We fully realise that this is an extremely small series of cases, and we have not included the results of 1,150 cataracts performed at Shikarpur in the six weeks immediately before our Khairpur clinic, because at Shikarpur there were six surgeons operating, several of whom were inexperienced. Therefore we feel that inclusion of their results would not lead to a fair assessment of the Smith operation.

In our clinic we use no sutures on the eye at all, neither superior rectus traction sutures, nor corneal nor corneo-scleral nor conjunctival flap sutures. We feel that the less the eye is interfered

with or traumatised, the better the results. We aim at simplicity and rapidity in our methods, which have been evolved to deal with a large number of patients in a short space of time. No patient with clinically clean eyes has any smear, culture, or other pre-operative investigation, and all are submitted to operation on the day of admission.

In this series we had no case of primary sepsis, and post-operative iritis was, practically speaking, absent. We attribute this freedom from sepsis to a double irrigation of the eye with 1/2000 solution of hydrarg. perchloride at operation coupled with the simplicity of technique and absence of meddlesome surgery.

Our vitreous loss was less than 3 per cent. in the intracapsular method, and this compares with a figure of just under 2 per cent. for our extracapsular cases at this clinic. The advantage gained for the lower vitreous loss of the capsulotomy cases is more than outweighed by the comparatively large incidence of iritis which occurs post-operatively in the extracapsular series.

We hope that this series of cases will convince a fair-minded reader that the adverse criticism which the Smith operation has received is quite undeserved. Moreover, we are convinced that the Smith operation, as outlined above, is the best operation for extraction of uncomplicated senile cataracts in the hands of the surgeon who has to deal with a large number of cases throughout the year.

AN OPHTHALMOLOGIST IN BUDAPEST AND PRAGUE*

BY

L. B. SOMERVILLE-LARGE

DUBLIN

LIKE many ophthalmological colleagues in Great Britain I received an invitation from the Hungarian Medical Trade Union to attend the Centennial Medical Week in Budapest from September 4th to 12th—but unlike them all I accepted. As a large number of British ophthalmologists will have happy memories of both ophthalmology in Budapest and of their Hungarian colleagues, a brief note of the meeting may be of interest.

The Centennial Medical Week covered the whole of medicine with ophthalmology as but one of 22 sections. The chairman of

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the ophthalmological section was Professor Horay, and the secretary Stephen de Grosz. The main subjects discussed were chemotherapeutics and ophthalmic instruments, although one was invited to choose freely of any subject. Official languages were Hungarian, English, French, German and Russian. Some 50 papers were allotted to the two days of the section's meetings, their duration being limited with an unaccustomed courtesy to " ten minutes for Hungarians and twenty minutes for foreigners." As, with the exception of a few papers in French and German and two in English, all were in Hungarian, I fear that my personal attendance was limited. The papers will be published in due course and need not therefore detain us.

British ophthalmologists may not recollect that the three Budapest professors best known to the English speaking world—Emil de Grosz, Imre and Blaskovics, have died comparatively recently. Their professorial appointments are now filled by Professor Horay and Professor Nonay.

I saw ward cases and attended operations in the First (Prof. Horay) and Second (Prof. Nonay) Eye Clinics and in the eye departments of the Istavan Hospital (Prof. Papolczy) and Janos Hospital (Prof. Csapody). In all four one was stimulated by witnessing exhibitions of faultless surgery, with, unhappily for the spectator, all too few complications. Marked variations in technique of cataract extraction were noticeable. In Prof. Nonay's clinic the retro-bulbar and lid injections were given half an hour before operation, but in Prof. Horay's and Prof. Papolczy's with the patient already on the table. In no case were the lashes cut, and in all the patient walked back to bed. In one clinic masks and caps were dispensed with. All used a superior rectus suture—controlled by an expert assistant throughout the operation. I only saw intra-capsular extractions—the standard procedure. The capsule was grasped at the " 6 o'clock " periphery and the lens withdrawn without side to side movements—the pressure on the limbus being relied upon to rupture the zonule. A single peripheral iridectomy carried out before extraction was the rule.

A sharp distinction was apparent regarding the advisability of corneal suture. The Imre suture is routine in Prof. Nonay's clinic, and even in his dextrous hands it adds ten minutes to the operation time. A variation of this suture is practised in Prof. Papolczy's clinic. Here, after the insertion of the suture, the section is made but is left just before completion. The conjunctival flap is then cut and finally the section completed with scissors. A difficult procedure, again taking some 10-15 minutes, but giving most beautiful results. Prof. Horay, on the other hand, uses no suture. Dr. de Grosz (son of Emil de Grosz) gave

a flawless demonstration of Blaskovic's operation for ptosis, and one envied his ability of explaining the steps through French, English and German. We were fortunate enough to see Prof. Csapody carrying out his well-known operation for contracted socket. It appeared a simple and highly satisfactory procedure in his hands.

As only a small number attended the operations, they were perfectly seen, and were a real pleasure to witness.

The doyen of the meeting was Prof. Pascheff of Sofia. This charming, widely-travelled specialist spoke to me of international ophthalmology from Moorfields at the beginning of the century to his own university in Sofia to-day. The visitor who came farthest was Dr. Pascal of New York. He intrigued us by describing a newer and better way to remember the actions of the ocular muscles. To my disappointment Filatov did not come to the meeting, and Russia was unrepresented.

Hungarian hospitality and courtesy is proverbial, to those indeed who have never been in Hungary they come as something of a revelation. To accept all invitations (official and private) was quite impossible, and perhaps my greatest regret was in having to omit Prof. Kettesy's kind invitation to his hospital at the old town of Debrecen in East Hungary. Prof. Weinstein's invitation to his department at the Jewish Hospital in Budapest had unhappily also to be left out of a full programme.

To the uni-lingual English speaker Hungarian ophthalmology is particularly satisfying as it is little exaggeration to say that every specialist speaks English, and the language is so widely read that the British Journal of Ophthalmology, Ophthalmic Literature, American Journal of Ophthalmology, and Excerpta Medica are in almost every clinic. The bond between British and Hungarian Ophthalmology is a very close one, and I can think of few better centres for a clinical tour (and few also where the Englishman would be more welcome) than Budapest, with the provincial clinics at Debrecen (Prof. Kettesy) and Pecs (Prof. Boros) not to be omitted.

In Prague I was fortunate enough to obtain introductions to the No. 1 and No. 2 Eye Clinics, and to Dr. Jermin's clinic at the Bulocka Hospital. Prof. Kadlicky of the No. 1 Eye Clinic has lately died and his place has not yet been filled. Dr. Dienstbier was kind enough to show me over the fine building and something of their work. Prof. Kurtz is now in charge of No. 2 Eye Clinic which used to be called "The German Clinic" when under Prof. Elschnnig. On the morning of my visit he was doing an operating list of some 55 cases. I timed one hour's operating out of the three I witnessed. In this period Prof. Kurtz did six

cataract extractions, a squint, a retinal detachment and an iridotomy. Fine theatre technique allowed operative technique to be unhurried. There were two tables in the one theatre, with ocular preparations mostly carried out by the assistants. The theatre was semi-darkened, two really excellent operating lamps of the reflecting type (made by Zeiss of Jena) gave a small brilliant light source over each table. Again I saw faultless intracapsular extractions, and again the lens was delivered with a straight rather than a zig-zag pull. For squint Prof. Kurtz does tenectomy with sometimes an advancement, sewing the muscle in its new position to the limbal lip of a zonal cut made into the sclera—a procedure which might appear somewhat dangerous. Orthoptic Clinics are absent in both Budapest and Prague. In retinal detachment operations the single point diathermy terminal was inserted through the sclera as often as was necessary and the sub-retinal fluid evacuated by scleral incision.

Prof. Kurtz is carrying out Filatov's subconjunctival placental inlay in large numbers of cases and for very many conditions. He also uses placental extract by subconjunctival injection. Retinitis pigmentosa is the only condition that at the present time he feels sure that these procedures assist. The placental tissue in a piece some 10-15 mm. x 4 mm. is embedded under the superior bulbar conjunctiva. This can be repeated in some three months. The placenta is untreated apart from being kept for 3-4 days at a temperature of 2°-4° centigrade. In these cases, although central vision is not improved, the field of vision fills out and " night vision " is assisted. In a general hospital that I visited these procedures are also being carried out, the placental tissue being inserted under the skin of the abdominal wall. Large numbers of cases are being done (100 on the morning of my visit) for conditions ranging from Dupuytren's contracture to duodenal ulcer, and from psoriasis to arthritis. Success is undoubtedly achieved, and it would appear that this form of therapy can no longer be neglected.

As in Budapest, so in Prague, hospitality and a courteous welcome were readily granted by one's colleagues everywhere, and everything done to make one's visit interesting and profitable.

OCULAR COMPLICATIONS IN ERYTHEMA EXUDATIVUM MULTIFORME WITH MUCOUS MEMBRANE LESIONS

(Pluriorificial Erosive Ectodermosis of Fiessinger and Rendu, Stevens-Johnson Disease, Baader's Dermostomatitis)* †

BY

J. E. WOLFF

ERYTHEMA exudativum multiforme is a specific skin disease of unknown aetiology which may be associated with various syndromes in which the mucous membranes—conjunctiva, lips, bronchi and ano-genital region—are affected, and consequently fall in the domain of the dermatologist, physician, ophthalmologist and uro-genital surgeon. As its name implies, erythema multiforme is characterised by the varied forms of its lesions. Hence no two cases are identical, and owing to the diverse characters of the syndromes a great deal of confusion has resulted in the literature. Authors in various countries had believed that they had discovered a new disease. Hence the multiplicity of names applied to the syndromes, as will be described below. We are in agreement with Sneddon who states that erythema multiforme and its syndrome represent different clinical entities, while Grove and Meisenhelder and others believe the syndrome merely to be a manifestation of erythema multiforme. Several articles on the subject have appeared in the last few years, so that our knowledge of the disease has increased.

A review of the subject shows that as long ago as 1822 Alibert and Bazin (quoted by Beaudonnet) noted that patients suffering from erythema multiforme sometimes presented a conjunctivitis. According to Steffens, Rigler gave the first detailed description of conjunctivitis complicating erythema multiforme in 1852. The name erythema exudativum multiforme was proposed by Hebra in 1866 to denote the erythematous skin lesions while Kaposi used the term "erythema polymorphe." The interesting earlier papers were by Fuchs (1876), Beaudonnet (1894), Düring (1896), Brault and Steffens (1902) and Salus (1912).

The origin of the names "pluriorificial erosive ectodermosis," "dermostomatitis" and "Stevens-Johnson disease" has been traced in the following manner: Rendu (1916). Fiessinger and Rendu (1917) saw a number of acute cases occurring in soldiers on the French front, and to these the name of pluriorificial erosive ectodermosis was applied (*see* also Berho).

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Some years later Fiessinger, Wolff and Thévenarch (1923), after seeing several more cases, divided the syndrome into two types—I and II. Type I presented the vesicles on the mucous membranes which were always accompanied by a skin eruption of iris-like lesions and purpuric spots, whereas in type II, the skin lesions are absent. The type II may be difficult to diagnose owing to the absence of skin lesions, though the acute onset of fever, stomatitis and ano-genital lesions and conjunctivitis are similar to the first type (de Lavergne).

In 1922 Stevens and Johnson described two cases occurring in children in U.S.A. and since then the syndrome has come to be known as Stevens-Johnson disease in the English speaking world.

Many papers bear the title of Stevens-Johnson disease, *e.g.*, Gilbert, Jones *et alia*, Urniker and Crofoot, Givner and Agelhoff.

In Germany a syndrome exactly the same as type I of Fiessinger was described by Baader in 1925 and since then has been known in German speaking countries as "Baader's dermostomatitis."

The aetiology of the disease is unknown, but four causes have been suggested:

1. E. Ramel suggested that it is due to a haematogenous tuberculous infection, but English investigators (G. H. Percival and H. Gibson; R. Hallum and J. W. Edington) were unable to confirm this by guinea-pig inoculations.

2. A virus theory has been considered by several authors though never proved. N. P. Anderson has discussed the relationship between herpes and erythema multiforme. I. Katzenellenbogen has suggested the use of vaccination in the allied disease of relapsing aphthous iritis.

3. Others have suggested that it is due to a vitamin deficiency, as some cases seemed to improve with vitamin B complex therapy (Adlorsberg).

4. An allergic theory has been stressed by some, because in northern countries the disease occurs most frequently in the spring and autumn. O'Donovan and Michaelson noted that their cases of epidemic kerato-conjunctivitis associated with skin lesions occurred during the rainy season in the Middle East. Bardella and Gandolfi found numerous eosinophils in the conjunctival secretions, but this has not been our experience.

Pathology. Biopsies have revealed a non specific inflammatory reaction.

Age. The disease usually affects people between the ages of 20 and 40 years, but Stevens and Johnson, Storck, Koke, Rosenberg, Wheeler, Edgar and Syverton, Dugan, Ginandes and Landolt have described cases occurring in children.

The disease is usually ushered in by a high fever, headache and prostration which might be severe, and is accompanied by an increase

in the leucocyte count and sedimentation rate. The stomatitis usually follows the onset of the fever, but may precede it in some cases (Murray). It presents three phases as a rule—erythema, vesicle formation and ulceration. A sero-sanguinous discharge or pus may develop. The genital lesions occur both in males and females, and consist of vesicles found on the glans penis and vagina. Nellen's case presented a purulent urethral discharge.

The skin eruption may be papular, macular, circinate, urticarial or haemorrhagic. As a rule it is symmetrically bilateral, with a predilection for the face, arms, legs, and dorsal surfaces of the hands and feet. (W. Stainsby).

The eye lesions of patients presenting a typical picture of erythema multiforme assume a bewildering variety of forms, and one can definitely state that there is no picture pathognomonic of the disease. Consequently the diagnosis has to be made by taking into consideration the entire clinical picture. In some cases conjunctivitis may usher in the disease (Düring, Grove and Meisenhelder).

The lesions vary from a mild conjunctival injection (Cocchi), often limited to the palpebral fissure, to a purulent conjunctivitis. Edmund divided the conjunctival affections into two types:—namely, fibro-membranous and papulo-vesicular. The frequency of conjunctival lesions may be judged from the statement that, of 122 cases of erythema multiforme, Düring reports that three-quarters showed signs of conjunctivitis. Vesicles, nodules, papules and pustules may form on the conjunctiva, and all forms may be present at the same time. Steffens, Terson, Nicolau, Düring, Beaudonnet and Barnett have described vesicles occurring in their cases, and both Steffens and Terson thought that it was a characteristic lesion of erythema multiforme.

Nodules have been noticed by several authors (von Benedek and Müller, Cottini, Alajmo, Bergmeister), and Alajmo studied a histological section which showed a lymphocytic infiltration. Von Benedek and Müller noted that the nodules in one case were situated at the limbus. Chaillious, Nobl and Steffens noted papules. Kubik noted papules, pustules and nodules in his two cases. A pseudo-membranous conjunctivitis is a relatively common complication, and Fuchs noted in a histological preparation of the membrane superficial, parallel layers of hyalin material, then a layer of fibrous exudate containing epithelial cells and round cells. Hanke's section was similar.

Cicatricial contractions of the conjunctiva occurred in our case to be described, and were also noted by Lever, Barkan and others. Symblepharon may form later.

In many cases the cornea is respected, but as in case I, corneal ulcer with perforation may occur. Loss of vision after perforation

Differential Diagnosis of Polymorphous Erythema, aphthous fever and relapsing aphthous iritis.

	Erythema exudativum multiforme			Aphthous fever	Relapsing aphthous iritis: Behcet's syndrome
	Classical type	Fiessinger-Rendu 1917 Stevens-Johnson 1922			
		Type I Baaders Dermostomatitis 1925	Type II		
Skin	Erythemo-vesicular eruption (relapsing)	Erythemo-vesicular (relapsing) eruption	No eruption	Erythemo-vesicular eruption especially seen on extremities	Papulo-pustular erythema or nodular erythema
Mucous membranes	Erythema-erosive lesion of lips, genitals, conjunctiva	Lesions of all the mucous membranes, including anus and bronchi	—	Erythemato-vesicular and erosive lesions of all the mucous membranes	Aphthous lesions of lips and anogenital region
Eye	Conjunctivitis-catarrhal, or papular, vesicular or pseudo-membranous, rarely an infiltrative or ulcerative keratitis, episclérıtis, kerato-conjunctivitis sicca	—	—	Catarrhal conjunctivitis, corneal infiltrations	Relapsing iridocyclitis with hypopyon, optic neuritis
Temperature	Slightly elevated	Elevated	—	Elevated	No temperature
Sex	Both	Males especially	—	Both	Males
Age	20–30 years	20–30 years	—	Any age	20–40 years
Blood	Leucocytosis (mononuclear) increased sedimentation rate	Leucocytosis (mononuclear) increased sed. rate	—	Leucocytosis increased sed. rate	No leucocytosis; sed. rate increased; hypoglycaemia, change in seroglobulin ratio
Duration	2–5 weeks	2–5 weeks	—	2–3 weeks	2–4 weeks—relapses frequent (often after months) during several years
Course	Various factors (intoxication, infective allergy)	—		Known virus	Seclusion and occlusion of pupil, vitreous opacities, blindness due to optic neuritis

has been reported by Bailey and Wheeler. Raffin's case developed a Descemetocele, the picture being complicated by a rhinitis as well.

Episcleritis is rather rare, but has been reported by Morax, Burnand and Lever. Hartley noted enlarged preauricular glands in one of his cases. Other complications will be described later.

The prognosis: all except one of Sneddon's cases recovered completely, but we feel that a guarded prognosis should be given in view of late sequelae which may occur.

The disease must be differentiated from ocular pemphigus, and recurring exudative iritis. It is easily diagnosed from the former, as pemphigus occurs in older patients as a rule, and has a protracted course, whereas erythema multiforme has an acute onset and recovery takes place from 3-5 weeks (Grove and Meisenhelder). The differential diagnosis is given in summary form in a table after Mach, Babel and Naville.

We now wish to present two cases which are follow-up studies, and have been noted in previous papers from our clinic by Mach, Babel and Naville, and later by Babel and Martin.

CASE I.—Mrs. A. M., born 1920. At the age of 20 years she became feverish, and a papulo-vesicular eruption appeared on her skin. A bilateral catarrhal conjunctivitis followed, accompanied by desquamation of the conjunctival epithelium. A corneal ulcer developed in the left eye, followed by perforation and incarceration of the iris. Complete recovery occurred in 2 months, except for an adherent leucoma in the left eye (Figs. 1 and 2).

In 1942 she returned to the Clinic complaining of bilateral ocular irritation. The lids of both eyes presented an identical condition—thickened, spongy and heavy, especially the upper lids. The lid margins were slightly inverted, causing some of the lashes to rub on the bulbar conjunctiva and the cornea. The bulbar conjunctiva, except for a slight redness due to that trichiasis, appeared normal On the contrary, the tarsal conjunctiva was thickened, very injected, and there were dense scars running parallel to and 2 mm. from the lid margin.

Left cornea—thickened opacity in the inferior quadrant with anterior synechia. Slit-lamp examination after fluorescein had been instilled into the conjunctival sac revealed some rather superficial erosions and desquamation of the conjunctival and corneal epithelium. Lacrimal secretion was slightly diminished. The entropion and trichiasis was corrected and the patient recovered.

In November, 1947, patient returned to clinic. Vision 2/50. Operation for division of anterior synechia was performed on November 12, 1947. On November 22, 1947, Professor Franceschetti performed a corneal grafting operation, and the cornea is clear, March, 1948 ; vision 0·3 with correction (Fig. 2).

CASE II.—Mrs. O. R., born in 1897. Nothing of importance in family or personal history, except for usual diseases of infancy.

On May 25, 1945, she suffered from a severe depression after the sudden death of her husband. On June 11, 1946, her temperature rose to 39°, and she developed a frontal headache. On the following day, it was noticed that her cervical glands became enlarged, and she complained of pain on swallowing, photophobia, lacrimation and rhinitis. On June 13, 1946: generalised exanthema, herpetic lesions in the throat, stomatitis, with slight oedema, expectoration of abundant mucus without coughing, oliguria, and constipation.

On June 14, 1946, the patient was admitted to the medical wards of the Hospital (Prof. Roch), with a temperature of 40·2° and an eruption of small spots on the face, trunk, knees and hands. On the face there was a tendency to confluence, on the arms there were slightly raised macules, in some of which a central vesicle later formed. The face was puffy, the lips swollen and dry, numerous small ulcers on

the buccal and pharyngeal mucous membranes, covered by a greyish pseudo-membrane and surrounded by an erythematous zone. Palpebral oedema. Severe injection of the conjunctiva with a moderate catarrhal secretion. Cervical glands enlarged and painful, but no other enlarged glands were found. The anal and vaginal mucosa were also swollen and studded with small ulcers.

Fig. 1.

(Case 1).—Photograph of the back of the legs showing typical erythema exudativum multiforme.

The cardio-vascular, pulmonary, neurological and urino-genital systems were normal. The various conditions thought of were: severe measles, severe polymorphous erythema, leptospirosis, a toxic or allergic eruption.

FIG. 2

(Case 1).—Photograph of the left eye after corneal graft.

FIG. 3.

(Case 2).—Photograph of the right eye showing scars and symblepharon of conjunctiva.

The cervical adenopathy disappeared in 1 week, though the temperature remained elevated. The skin commenced to desquamate. On June 30, 1946, the temperature was subnormal and on the buccal mucous membranes—large plaques dark, red in colour, which bled easily on touching, were noted. The cutaneous elements took on a *café*

au lait colour. Slight desquamation occurred on the trunk, while on the hands and feet large scales formed. The conjunctivitis, at first catarrhal, became muco-purulent, and later pseudo-membranous. Examination of the secretion revealed no pathogenic organisms.

Chest X-ray July 8, 1946—bilateral exudative hilitis with foci of exudation at both bases. August 1, 1946, exudation had disappeared, but tiny nodules were visible in both apices (T. B.?)

Blood pictures: W.R. negative.

Slight increase in sedimentation rate.

Slight increase in icteris index.

Agglutination for various type of leptospira negative.

Paul-Bunnel test negative.

Takata test negative.

Calcium: 9·6 mgm. %.

R.b.c 's.: 3'900 000.

W.b.c.'s.: 9'500 on June 14, 1946; 3'100 on June 18. 1946; 6'500 on July 10, 1946; 7'800 on June 26, 1946.

Mononuclear: 36 per cent., slight eosinophilia.

January 15, 1947: R.b c.'s,: 4'260'000: Hb.: 48 per cent. C.I.: 1. W.b.c.'s.: 4'800; 50·5 per cent. poly neutrophils; 7·5 per cent. immature forms, 1 per cent. eosinophils; 0·5 per cent. basophils; 29·5 per cent. lymphocytes; 11 per cent. monocytes.

Urine: Intermittent traces of albumin and sugar, some leucocytes. No micro-organisms found in skin lesions. Inoculation into the cornea of a rabbit: negative.

On July 31, 1946, the patient was discharged from the hospital, her general condition being good. In the beginning of August, we noted for the first time some infiltration in the centre of the right cornea, and intense mixed injection of the right eye, moderate injection of the left eye. The abundant secretion presented the following characteristics: thick, whitish, viscid filaments. No micro-organisms or inclusion bodies. Staph. albus on culture. Vision 1/10 on both sides. A mild irido-cyclitis more marked on the right side was present. In September the secretion remained the same. The Meibomian glands easily visible, and their ducts were enlarged. The corneal ulcer had commenced to heal. The irido-cyclitis had disappeared on the left side, but there was still some K.P. on the right side. A symblepharon was noticed forming near the punctum of the right lower lid. The appearance of whitish bands, 1 mm. from and parallel to the lid margins was noted. In October, though the cornea had healed, deep vessels began to invade the parenchyma The conjunctival bands did not progress, but the abundant secretion continued. In December a similar invasion by blood vessels of the left cornea occurred. This eye had in the meantime suffered from an attack of irido-cyclitis which rapidly healed, while the right irido-cyclitis had almost completely disappeared. The conjunctival secretion became a little less profuse. On installation of Bengal rose and fluorescein tiny ulcers became apparent in the conjunctiva and corneal epithelium. The lacrymal secretion became almost completely abolished.

At the time of writing the condition has become stabilised. The lids are still thickened, there is a slight viscid secretion on the right side. The corneal ulcer and uveitis have gone. The conjunctival scars and symblepharon remained stationary.

Summary

A review of the literature has revealed that almost any ocular complication can occur in the syndrome of erythema multiforme from a mild injection of the conjunctiva most marked in the palpebral fissure, a catarrhal conjunctivitis, a membranous or purulent conjunctivitis. Younger people seem to be more prone to the purulent type. Corneal involvement is comparatively rare. Finally, panophthalmitis may occur. Lesions affecting the conjunctiva

appear to be the most frequent sequelae of the disease, and one should watch the patient for a long time lest symblepharon should occur. An accurate prognosis is thus impossible, and our experience has not borne out the statement that the mucous membrane lesions are always benign (Genet and Speckmann). Herpes ophthalmicus, which is almost certainly due to a virus, is known to affect every ocular tissue, and if the erythema multiforme syndrome is also due to a virus, while the organism shows a predilection for the mucous membranes, it may affect any tissue.

While the ætiology remains obscure the treatment is necessarily symptomatic. Reports of the use of vaccination are too scanty to permit any judgment on its effect. Sulphonamides and penicillin may assist in preventing or curing secondary bacterial invasion. Corneal grafting may be performed. It was done in the first case described in this paper, and we believe it to be the first time this operation has been performed for corneal lesions due to erythema multiforme. These remarks have been illustrated by the description of two cases.

Case I returned to our clinic two years after an acute attack complicated by the development and perforation of a corneal ulcer in the left eye, presenting a trichiasis due to entropion, and small dense scars in the tarsal conjunctiva. The entropion was corrected, and three years later she returned. Corneal grafting was performed, and the vision, which was 2/50 owing to a leucoma, is now 0·3 with correction. We believe this is the first time a patient has undergone the operation for leucoma complicating erythema multiforme.

Case II presents several interesting features. The first attack occurred at the age of 49 years, whereas the disease most commonly attacks people of the 20-40 year age group. The patient's general condition was very grave. Chest complications are very rarely encountered, though two other cases have been cited—one of Kove's patients who was gravely ill developed a broncho-pneumonia, and Nellen's case a transitory pulmonary consolidation. The recurrent attacks of irido-cyclitis resembled those which occur in relapsing aphthous iritis (Behcet's syndrome) —*vide* table of differential diagnosis. The alteration in the lacrimal secretion and the punctate staining on instillation of Bengal rose and fluorescein is typical of kerato-conjunctivitis sicca, but unlike the "idiopathic" form, this complication was presumably due to involvement of the secretory glands of the conjunctiva. This complication is not unknown because Richards and Romaine, Richards and Grossmann have reported kerato conjunctivitis sicca as a late manifestation occurring in cases of erythema exudativum multiforme.

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CONICAL CONTACT LENSES

BY

G. D. McKELLEN

CONICAL contact lenses—*i.e.*, contact lenses having haptics in the form of a truncated cone—were designed and first produced by Dr. William Feinbloom, of New York, who described them in an article in the "Optometric Weekly" in 1945. Dr. Feinbloom stated in that article that the major problem in contact lens fitting has always been that of reducing to a minimum the pressure of the lens on the eye. He was using Zeiss ground lenses with spherical haptics prior to 1930, and read a paper dealing exhaustively with this type of lens at the American Academy of Optometry meeting in Omaha in 1930. After ten years' experience with this type, he changed over to the moulding method, which he described in a paper at the Academy meeting at Chicago in 1936.

After carrying out this technique on some thousands of eyes, he decided that it was easier to carry out the necessary grinding and adjusting on standard lenses of a shape more truly representing the shape of the eye than spherical lenses. Study of the moulds taken, showed that the curves of the surface of the eye are toroidal rather than regularly spherical, and he developed a series of lenses with toroidal haptics in 1940. He says that " While these lenses gave results that were a significant advance on those given by the older types, he was still dissatisfied." He then stated the problem thus—" What form should the haptic of a contact lens take in order to produce minimum pressure on the sclera and conjunctiva?" And " At what places should the lens rest on the sclera so that the pressure remains minimal, even when the lens moves?" A long series of experiments was undertaken to determine the effects of changes of surface forms, and the main conclusions arrived at were :—

(1) the surface used must rest on an area sufficiently behind the limbus to avoid pressure there;

(2) this surface must be sufficiently inside the edge of the lens to prevent the edge from digging when worn for a long period of time;

(3) this surface must rest on an area narrow enough to allow change to a new area as the eye moves;

(4) if the lens rests on the prescribed areas, then the more tangential the surface of the haptic is to the eyeball, the less the pressure on the eye.

Thus the " conical " haptic was arrived at, and " Feincone " lenses were introduced. A " Feincone " lens is made up of three parts—the spherical " optic," the conical " haptic," and a temporal flange. The purpose of the flange is to carry the temporal edge into the outer fornix and bring it into bare contact with the bulbar conjunctiva, so that it does not rub the lid margins at the outer canthus where the lid pressure is greatest. A noticeable feature of the conical lens is the almost complete absence of the transition shoulder or ridge that can be felt in other types. This, I think, is an important point to which I will refer later.

There are five variables in the conical lens :—

The angle of the cone.
The radius of curvature of the flange.
The overall size.
The radius of curvature of the optic.
The diameter of the optic.

The cone angle determines the position of the area of contact of the haptic for a given eye. The smaller the angle of the cone,

the further back the area of contact. Compare Fig. 1 with Figs. 5 and 6.

In the Feincone series the angles are 80 deg., 86 deg., 92 deg., 98 deg., 104 deg. and 110 deg., though they are specified by the half-angle—40 deg., 43 deg., 46 deg., 49 deg., etc. The most commonly used angles are 43 deg. and 46 deg.

The flange radii are 12 mm., 12·6 mm., 13·2 mm. and 13·8 mm.

The "standard" overall size is about 23 mm., but smaller and larger lenses can be obtained, specified + or − 1, 2, 3, 4, or 5.

The radius of curvature of the inner surface of the optic is normally 8·5 mm. in the 40 deg., 43 deg. and 46 deg. angles, and

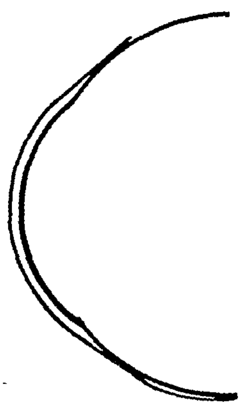


FIG. 1.

A well-fitting conical lens.

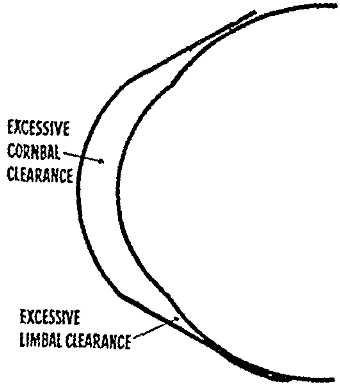


FIG. 2.

Lens of too small an angle of cone.

8 mm. in the 49 deg., but any radius from 7, 7·5, 8, to 8·5 mm. is obtainable with any angle.

The normal diameter of the optic is 12 mm., but the whole series can be obtained with 14 mm. diameters if required. This is an advantage in certain cases—those having unusually large corneae.

There are also double-angle lenses which are useful for large flat eyes (Fig. 3).

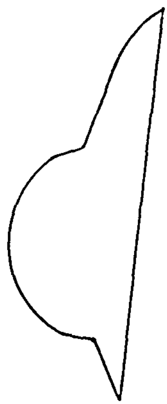


FIG. 3.

Double-angle haptic.

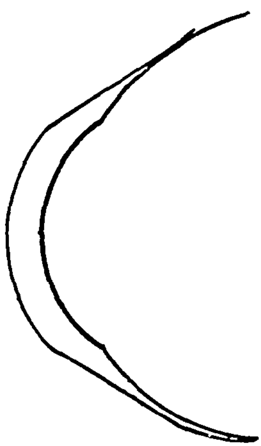


FIG. 4.

Showing tight flange. Note how lens is lifted so that haptic does not rest on sclera.

The fluorescein test is used to determine the correct angle of cone and radius of curvature of the optic. The aim is to put the band of contact two or three millimetres behind the limbus and to give positive corneal clearance with the eye in the primary position (see Figs. 1 and 5).

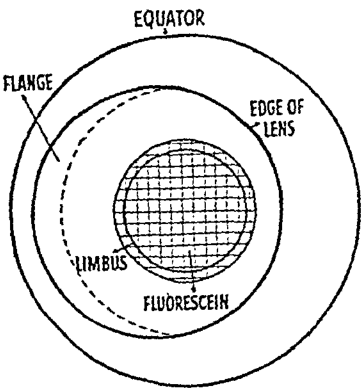


FIG. 5.

Lens on eye, frontal view. Showing *minimum* limbal clearance.

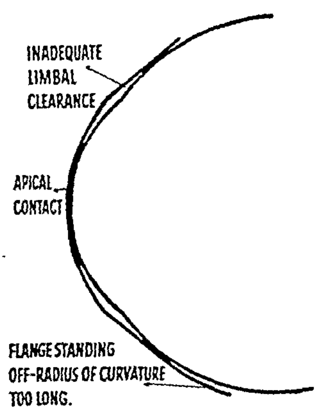


FIG. 6.

Angle of cone too great.

The limbal clearance must not be too great, or the lens tends to edge contact and lags badly, and protrudes too far, giving a poor cosmetic effect (Fig. 2). The lens should be allowed to remain *in situ* for half an hour before final judgment as to the correctness of the selected cone angle is pronounced. In some cases the lenses settle back quite a lot—owing probably to the thickness, looseness and texture of the conjunctiva and episcleral tissue.

While selecting the cone angle it is necessary to watch the flange also. If the flange is too steep so that it digs, the whole lens may be lifted so that the cone does not make contact in the normal manner, even though it is of the correct angle (Fig. 4). The fluorescein will then extend right to the periphery. The flange should make *bare contact with the conjunctiva.*

When the correct angle of cone, radius of flange and radius of curvature of the optic have been chosen, any sensation the patient reports will be due to the rubbing of the lids against the edges of the lens. This may well be due to wrong over-all size, and the same lens of smaller or larger diameter should be tried. In some cases—usually cases of rather marked irregularity of the surface of the globe—there may be a loose edge at one localised part, necessitating either grinding off or bending with the " Feincone " forceps—a forceps with parallel jaws curved to approximately the curves of the haptic, which is heated in boiling water and applied to the area to be bent. In the hands of an experienced operator these forceps are of very great value, eliminating the need for much grinding, etc. Feinbloom's own instructions regarding examination of the edge fit are :—

Examine the edges in ordinary light in this order :—

(a) Superior—if tight (blood vessels interrupted and conjunctiva blanched) angle of cone is too small. If loose but no loss of liquid occurs, ignore.

(b) Superior-nasal—this must not be tight or it will certainly cause trouble. If tight, increase angle. If loose, without loss of liquid, ignore.

(c) Nasally (at 180 deg.)—should be loose without loss of fluid. If tight, increase angle of cone.

(d) Temporally—flange edge must *just* rest against conjunctiva. If tight, increase radius of curvature of flange. If standing off, decrease radius of curvature of flange.

A good method of showing that the sensations described by the patient are due to lid irritation is to lift the lid away from the lens at the point indicated by the patient as being " tight " or otherwise uncomfortable. If the sensation disappears as the lid is lifted away, it is almost certainly pure " lid-sensation," due to rubbing of the palpebral conjunctiva against the edge of the lens. The edge of the lens may need adjustment, or the sensation may pass away after a few minutes. A patient with tight lids will feel the edges of the lenses more than one with loose lids, and due allowance must be made for this factor. Repeated insertion and removal of the lenses is the best remedy for tight lids.

A well-fitted conical lens should be worn for four hours at the first attempt, without any discomfort.

Conical lenses are now being made in England. The only

English-made ones of which I have experience are the " Kelvin " lenses made in Manchester. They are based on the same principles as the " Feincone " lenses, but are made of a harder plastic, and are thinner. The flange is not spherical in curvature—its curve is, I believe, hyperbolic in form—and this has reduced the " hump " at the temporal side. The flange curves smoothly from the haptic and follows the curve of the sclera closely. The " Kelvin " series provides a rather larger range of cone angles, 84 deg., 88 deg., 92 deg. (the same as the " Feincone " 46 deg.) 96 deg., 100 deg., 104 deg.—*i.e.* in steps of 4 deg. instead of 6 deg. Each cone angle can be obtained with radius of curvature of optic of 7 mm., 7·5 mm., 8 mm. or 8·5 mm., as required. The flange curvatures vary from 12·25 mm. to 14·5 mm. radius. The optic is decentred bodily towards the nasal edge, the standard decentration being 12½ deg., which can be varied to 14·5 deg. or 10·5 deg. The 10·5 deg. decentration gives more material nasally and less temporally : the 14·5 deg. gives less nasally and more temporally.

" Double-angle " lenses are available in The " Kelvin " series. These have two different angles of cone in meridians at right angles to each other. The meridians can be at any position—say 180 deg. and 90 deg., 45 deg. and 135 deg., 60 deg. and 150 deg., etc. The effect is a " squashed " cone which will fit a " toric " sclera. A regular cone will fit a toric sclera if the toricity is not too great. The fluorescein pool will be oval, with the long axis of the oval along the meridian of steepest curvature, in such a case, but this does not matter so long as the band of contact does not reach the edge of the lens. In some of these cases it is necessary to fit an oval lens, *e.g.*, instead of 23·5 mm. diameter, 24·5 × 23·5 mm., long axis vertical. This would be sufficient to take care of a mild toricity. If the eye cannot be fitted satisfactorily this way, a double-angle lens—say LF (96 deg. and 92 deg.) should be tried, and if this difference is still not enough, the LE (96 deg. and 88 deg.) should be tried, and so on. These double-angle lenses are most useful, and differences up to 16 deg. are provided. Any scleral toricity of such degree that the double-angle lenses with 16 deg. difference will not cope with it, indicates the need for moulding. The double-angle series will cope with scleral toricity far beyond the range of oval ground sphericals.

My own experience with conical lenses has satisfied me that there is a definite place for this type in the armoury of every serious practitioner. The fitting technique is a good deal simpler than any other and takes much less time, which is an advantage from the patient's point of view, at least. I believe that 50 per cent. of the would-be wearers of contact lenses can be fitted with conical lenses with results at least as good as those of any other method—

in some cases with better results, because some eyes are of a shape that is ideal for the conical lens and less suited to any other type. If 50 per cent. of one's patients can be satisfactorily fitted by a method that takes half the time required for any other, it would be stupid not to use it. I am not advocating hurried work, but I do feel that any technique that shortens the time required for *satisfactory* fitting is to be encouraged.

It is also true that there are some eyes that cannot be fitted satisfactorily with conical lenses or can better be fitted with other types. No attempt should be made to fit these cases with conical lenses, and if necessary, they should be referred to other practitioners who are masters of the more difficult techniques of fitting moulded and ground spherical lenses.

There is no doubt that, for a recruit to contact lens fitting, the conical type is the easiest and least expensive to begin with, and will cover a wider range of patients satisfactorily, than will any other type. Nevertheless, the aim of all practitioners should be to fit all types. Fitting conical lenses will enable the beginner to gain confidence and experience for the more difficult work.

Conical lenses are extremely comfortable to wear, it is relatively easy to obtain a perfectly comfortable fit. This is due in part, I think, to the absence of the transition ridge, and partly to the fact that the lens rests well behind the limbus on a narrow band of conjunctiva, and changes its position of contact slightly as the eye moves. The veiling problem does not seem to be eased appreciably by the use of conical lenses. One gets the same widely varying results as with other types. Conical lenses lend themselves to experiments along the lines of fenestration, grooving of the haptic, etc., as well as any other type, but no considerable work has been done in this direction so far.

The last word on contact lens design has not yet been said, but the use of conical lenses will no doubt lead to some further developments. I would say, from my own experience, that the advent of conical lenses has advanced the science of contact lens fitting, and provided us with a simple and less *time-consuming method* of obtaining a comfortable and satisfactory fit for a large percentage of our patients. It has shown that the "glove fit" is not necessarily the correct ideal to strive for, and that a design far removed from the moulded lens may yet prove to be the answer to some of the problems with which we are faced.

POST-OPERATIVE SECURITY IN CATARACT OPERATION

BY

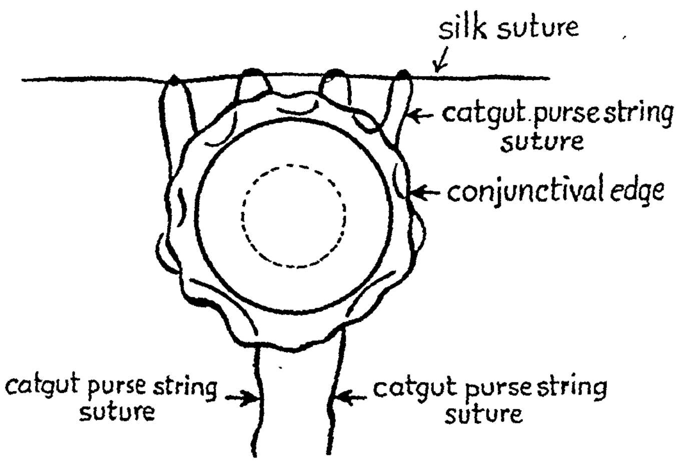
T. G. WYNNE PARRY

BANGOR

SINCE the article on a method of providing post-operative security in cataract operation was published in the September, 1947 issue of the *Brit. Jl. Ophthal.*, some colleagues have mentioned the difficulty of carrying the upper part of the complete conjunctival flap over the wound when drawing the purse string suture tight after the extraction. The edge of the flap, unless guided carefully by an iris repositor or similar instrument, in some cases entered between the lips of the section.

For some time past the following procedure has been found to work very well, and to give complete control over the upper part of the conjunctival flap, no matter how widely the section may gape.

A silk suture, No. 0, in a curved needle—a blunt one is preferable—is passed through each loop of the purse string suture from



9 o'clock to 3 o'clock (see diagram), the ends of the suture are left loose on both sides.

When the extraction is completed, and the toilet of the wound is finished, the silk suture is drawn taut, this draws the upper half of the conjunctival flap towards the suture and then, while the purse string suture is tightened, the silk suture simultaneously is carried forward and down over the wound, taking the conjunctival flap with it.

When the purse string suture is tied and cut, the silk suture can be similarly dealt with. With this silk suture holding the whole of the upper half of the conjunctival flap, the control of the flap is so complete that any section, even when gaping with vitreous loss, can be covered without difficulty.

With regard to fixation of the globe for section when this method of complete conjunctival flap is used, Mr. Williamson-Noble has suggested to me that an episcleral suture, as used by him, gives good control, etc., and is possibly preferable to the original suggestion of leaving a conjunctival tag at 6 o'clock on the corneal margin. I have not yet tried this method, but it would certainly seem to allow of a cleaner conjunctival flap and more certain fixation. I am indebted to him for his suggestion.

BOOK NOTICES

Physiology of the Eye. H. DAVSON. Pp. x and 451. 301 Figs. Bibliography. London: J. and A. Churchill. Price 32/-. 1948.

This book, in the words of the author's preface, has been written with the needs of the medical student, the optician, and the prospective diplomatist in ophthalmology in mind. It is clear that a knowledge of the fundamental principles of ocular physiology is an essential item in the clinician's armamentarium, but, while in recent years there has been produced a plethora of monographs and original papers on various aspects of these principles, there has equally during the same time been published no book attempting to give a balanced conspectus of new work. The book under review not only describes simply but fully the established facts of ocular physiology, but gives a fair and balanced, though condensed, assessment of new work and its implications.

After a simply written introduction on the structure of the eye, the first two sections deal with intra-ocular dynamics and the mechanism of vision. Both these subjects at the present time are in a state of flux such as would rejoice the followers of Heraclitus, and one need only say that on such contentious theories, among others, as those on the physiology of the intra-ocular fluids, the photochemical aspects of vision, and colour vision, the author gives a fair and up-to-date summary.

The following sections discuss the neuro-muscular control of the extra-ocular muscles, of the pupil and of accommodation, the protective mechanisms of the eye, visual perception and elementary physical and physiological optics. In the section on optics, the exposition is as simple as possible; complicated mathematical

formulae have been avoided as far as reasonable, while the optical principles have been made adequately clear in a series of well-drawn ray-tracing diagrams.

Within its self-imposed limitations the book is excellent. It should be warmly welcomed and well received by the prospective examination candidate, and by those of his seniors who wish to take, as it were, a "refresher course" which embraces the essentials of modern work and views.

NOTES

Royal College of Surgeons of England. Ophthalmology Lectures

THE following lectures will be delivered at the College in Lincoln's Inn Fields, London, W.C.2:—*Tuesday, March 29, 1949*, Professor A. Franceschetti (Prof. of Ophthalmology, University of Geneva), Cataract Associated with Lesions of the Skin, at 5 p.m.; Professor G. B. Bietti (Prof. of Clinical Optics, Pavia University), Ophthalmic Aspects of Protein Deficiency and Disordered Protein Metabolism, at 6.15 p.m. *Wednesday, March 30, 1949*, Dr. E. Hartmann, Psychosomatic Symptoms in Ophthalmology, at 5 p.m.; Professor H. J. M. Weve (Prof. of Ophthalmology, Rijksuniversiteit) (the subject to be announced later), at 6.15 p.m.

W. F. DAVIS,
Secretary,
Postgraduate Education Committee.

Papers submitted for publication should be sent to :—

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Such papers should be typewritten in double spacing on one side of the paper only, leaving a $1\frac{1}{2}$ inch margin. The Author's name and address should be plainly indicated. References to the literature should be set out in accordance with the Harvard System, *e.g.*, Langley, J. N. (1919).—*J. Physiol.*, **53**, 120. Illustrations should not be fixed to the typescript. They should be numbered in sequence, and the top of each should be clearly marked.

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THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

MARCH, 1949

COMMUNICATIONS

THE EYES IN MONGOLISM

BY

RONALD F. LOWE

MELBOURNE

From the Institute of Ophthalmology, University of London

LANGDON DOWN in 1866 postulated that certain groups of idiots gave indications of a regression from one racial type to another. In stating that "a very large number of congenital idiots are typical Mongols" he gave a name to one particular group. Langdon Down was influenced by the appearances of the face and especially by the shape of the palpebral fissures. His clinical observations were shrewd but his racial comparisons were very superficial and unfortunate.

For centuries mongolism and cretinism had been considered to be the same abnormality, but during the latter half of the last century many contributions from distinguished observers enabled the two conditions to be separated.

Although mongolism is now recognised as a definite clinical entity it is most important to remember that there is no single diagnostic sign. Like all syndromes its recognition depends on a

number of stigmata, each of which varies between individuals. Tredgold (1947) stated : "Many ordinary aments and even normal individuals possess one or more of the peculiarities which go to make up mongolism. It is the combination which is characteristic."

The appearances of the eyes were among the first abnormalities to be recorded, and in this small region there are several characters which may assist diagnosis in doubtful cases. The purpose of this paper is to review these signs and extend the descriptions to cover many aspects only briefly reported in the past.

GROWTH

One of the most important changes in mongolism is the retardation of growth affecting almost the whole of the body. This feature was recognised by Séguin in 1866, and has received considerable attention from most writers. The deficiency is well described by Benda (1946) in his book "Mongolism and Cretinism." He reviews many aspects, and emphasises that although at birth the mongoloid baby is little smaller than normal, within the earliest years of life the difference becomes very striking, so that the mongoloid always remains considerably retarded. Many observers consider that there is a tendency to retention of foetal characters throughout life in mongolism. As the mongoloid is so much slower than the normal in development, numerous foetal and infantile characters are outgrown later, but many disappear if given sufficient time. In the past very few of these patients lived for many years, but with extended control of so many infectious diseases, and the great improvement in institutional life, the mongoloid now attains a much greater age.

In the present series of 67 patients examined, 40 were over 25 years of age and the oldest was over sixty.

THE SKULL

Four skulls of adult mongoloids were examined in the museum at Leavesden Hospital. They were prepared by Dr. R. M. Stewart when he was physician-superintendent. Their ages were as follows—case 68, aged 31 years; case 69, aged 35 years; case 70, aged 42 years; and case 71, aged 52 years.

Although these patients had lived well into adult life, all the skulls were remarkably similar in showing features which normally disappear during the second or third years. Abnormalities were prominent where marked changes occur with normal growth after birth.

All skulls had persistent metopic (frontal) sutures. The foramen lacerum medium was widely open in three skulls (Fig. 1, Cases

No. 69, 70 and 71). In these the foramen ovale communicated freely with the foramen lacerum medium, while the foramen spinosum was not quite cut off. Foramina of Huschka were present in all tympanic plates.

In the accessory nasal sinuses development was very limited. The small maxillae and orbital ridges are obvious in the frontal and lateral photographs. This lack causes the flattened appearance of the face so well seen in life. In contrast with the other nasal sinuses, the ethmoid air cells were well developed in every skull (Fig. 4, Case No. 71).

The nasal bones varied in size but were always smaller than normal; sometimes they were almost absent (Fig. 2). In life the height of the nasal bridge is very variable. Usually it is flattened, but quite a number are of practically normal elevation.

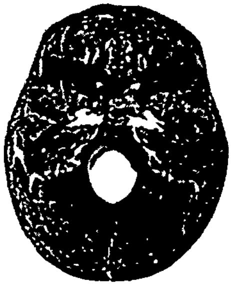
The general thinness of the skull bones has been recorded by other observers (Greig, 1927; Benda, 1946). It was conspicuous in these specimens, and the orbital plates were very thin. The superior and inferior orbital fissures were very wide.

The characteristic shortness of the sagittal diameter is clearly visible in the photographs. It gives each skull a flattened and broadened appearance. In this shortening the orbits are somewhat reduced in depth, but their shallowness is not as obvious as expected.

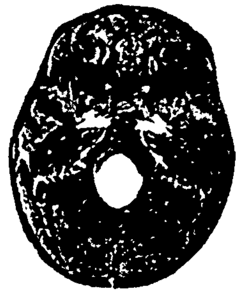
The antero-posterior orbital axes of normal skulls are inclined to each other at an angle of about 45 degrees. In mongolism, because of the relatively greater diminution of the antero-posterior axis compared with that from side to side, the orbital axes are inclined at about 75 degrees. This follows because the apices of any orbits are very close to their medial walls, and as these measuring points move forwards the angle between the diverging axes increases. The angles measured in the four skulls were as follows: in case 68, 70 degrees; in case 69, 70 degrees; in case 70, 75 degrees: in case 71, 80 degrees. In all the skulls the horizontal orbital axes definitely sloped downwards and outwards as is normally found in European skulls. Although Whitnall's orbital tubercle could be readily identified as being higher than the attachments of the medial palpebral ligament, any change in relationship between the orbital bones could not be found as an underlying cause.

The cribriform plate was deeply sunken between the orbital roofs, giving a more oblique slope to the upper parts of the medial orbital walls and indicating considerable disturbance of growth in this region.

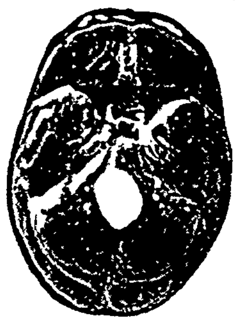
The skulls contain so many peculiarities that it is difficult to separate the secondary effects from those of a more fundamental nature.



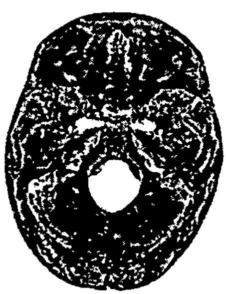
Case No. 69, age 35 years.



Case No. 71, age 52 years.



Normal European adult.



Case No. 70, age 42 years.

Case No. 68, age 31 years.

FIG. 1.

The floors of the skulls of one normal and four mongoloid adults.

The mongoloid skulls show general bony thinning, reduced antero-posterior diameter (brachycephaly) and absent frontal sinuses. The foramen ovale communicates with the foramen lacerum medium in Cases No. 69, 70 and 71.

Case No. 69, age 35 years.

Case No. 71, age 52 years.

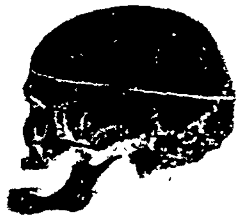
Normal European adult.

Case No. 70, age 42 years.

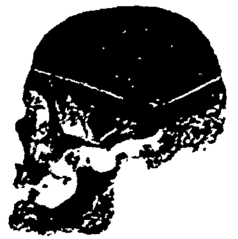
Case No 68, age 31 years.

FIG. 2.

Frontal views of the skulls of one normal and four mongoloid adults.
The mongoloid skulls show persistent metopic (frontal) sutures, wide orbital fissures, very small nasal bones and maxillae.
All horizontal orbital axes slope downwards and outwards.



Case No. 69, age 35 years.



Case No. 71, age 52 years.

Normal European adult.

Case No. 70, age 42 years.

Case No. 68, age 31 years.

FIG. 3.

Lateral views of the skulls of one normal and four adult mongoloids. The mongoloid skulls show smallness and flattening of the facial structures

FIG. 4.

The medial wall of the left orbit of mongoloid No. 71, showing well developed ethmoid cells.

THE PALPEBRAL APERTURES

The shape of the palpebral apertures has attracted attention for many years, and it was their appearance which was especially noted by Langdon Down when he introduced his Mongol hypothesis. This region has been frequently described, but some aspects still require a correct interpretation. Normal Europeans have the outer canthus slightly higher than the inner, and occasionally this difference may be accentuated sufficiently to give the appearance of a definite slant. From a large number of photographs of members of the true Mongolian races, Gifford (1928) found that the slope of their palpebral fissures was no greater nor any more frequent than in his own non-Mongolian patients. He concluded that the slant eye of the true Mongolian is a myth, and that instead the narrow or slit-eye is more characteristic.

Komoto (1892), writing of Japanese, stated that an epicanthus exists physiologically among them, and this gives an appearance of obliquity as it passes downwards and across the inner angle.

The eyes of the true Mongol have an almond shape due to the widest part being towards the inner angle; with the long palpebral aperture narrowed and tapered laterally. This is quite different from the mongoloid. The outstanding features of the mongoloid

palpebral apertures are obliquity and shortness (Figs. 5, 7 and 9). Less commonly narrowing is also present. The obliquity may be very pronounced, but occasionally it is absent. There is often some asymmetry between the two sides of the face.

The characteristic shortness of the palpebral apertures has been frequently recorded. The combination of obliquity and shortness

FIG. 5.

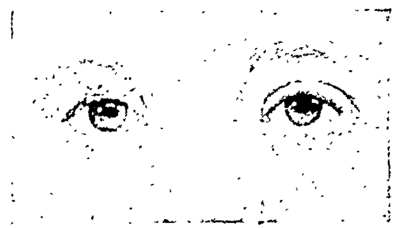


FIG. 6.

Fig. 5. Case No. 26, aged 20 years. Typical mongoloid palpebral apertures showing obliquity upwards and outwards, shortness, and even arch of upper lid margins.

Fig. 6. Case No. 40, aged 32 years. Mongoloid adult showing persistent epicanthus. The upper lid margins are evenly arched although the palpebral apertures are horizontal.

FIG. 7.

FIG. 8.

Fig 7. Case No. 50, aged 39 years. Showing very short sloping palpebral apertures and flat nasal bridge, usual appearance without epicanthus.

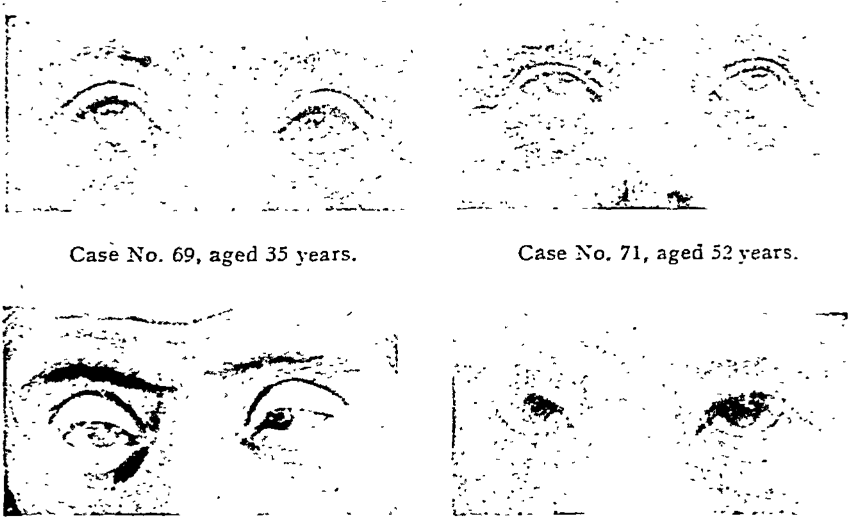
Fig. 8. Case No. 50. Demonstrating loose skin over nasal bridge. Stretching from below produces folds like epicanthus.

quickly draws attention to this region of the face. Often the palpebral apertures are described as narrow, but narrowing is not particularly common unless there has been an underlying infective process. Trachoma has been the commonest cause because it produces ptosis, or swollen lid margins from chronic discharge.

The curve of the upper lid is worthy of description. Normally the upper lid margin has its highest point at the junction of the inner and middle thirds. The mongoloid upper lid has a much more gradual and even curve so that its highest point is at the

centre. This peculiarity in shape is seen whether the palpebral aperture is horizontal or oblique. The even arch is occasionally seen in normal adults, and is fairly common in those conditions involving disturbed growth of the head.

The cause of the obliquity of the palpebral apertures has received explanations that are unsatisfactory. Van der Scheer (1918)



Case No. 69, aged 35 years. Case No. 71, aged 52 years.

Case No. 70, aged 42 years. Case No. 68, aged 31 years.

Fig. 9.

The palpebral apertures of the four mongoloid adults whose skulls are shown in Fig. 2.

The slope of the palpebral apertures is in the opposite vertical direction from that of the horizontal orbital axes.

considered the cause was dwarfism or absence of the nasal bones, the frontal bones sending processes downwards to make up the defect, carrying with them the covering tissues. Although the four skulls examined all had nasal bones smaller than normal, no downgrowths of the frontal bones could be seen. If the obliquity were dependent on the smallness of the nasal bones it should be present in many normal babies. This is not so, and European babies show no more obliquity than the adults.

From numerous X-rays of young mongoloids, Benda (1946) reported the presence of egg-shaped orbits with a slope of the orbital axes upwards and outwards. He inferred that the bones cause the palpebral apertures to follow the same direction. But the four adult skulls here reported all had orbital axes that inclined definitely downwards and outwards, as is normal in Europeans.

Photographs of these patients taken during life show the presence of oblique palpebral apertures in all (Fig. 9). The slopes are undoubtedly in the opposite vertical direction from those of the orbital axes.

In the museum of the Royal College of Surgeons of England, an examination was made of the faces of 25 foetuses of gradually increasing development from 2 months to birth. A similar examination was made of 20 foetal skulls of the fifth month and later.

At the second foetal month the eyes are directed laterally, and the apertures between the developing lids slope markedly upwards and outwards. In the following month the eyes develop a more frontal direction, and the lid edges become apposed, although the line of fusion is clearly visible. These lines on each side assume a more horizontal direction, so that by the fourth month, when the eyes are almost directed forwards, the lids are inclined only slightly upwards and outwards. By the fifth month the eyes have reached their frontal positions and the lid lines are horizontal. The eyes and palpebral apertures maintain these relations throughout life.

During the fifth month, when the palpebral apertures have already reached their permanent stations, the horizontal orbital axes are still directed upwards and outwards. Their inclination likewise changes with growth. By the sixth month the slant has almost disappeared, and at the seventh month the alignment is straight. At birth most orbital axes slope downwards and outwards, but some are still horizontal. The change continues during postnatal development, and is conspicuous in almost all European skulls.

The upward slope of the orbital axes observed by Benda appears to be a retardation of development so commonly seen in mongolism, but in time the anomaly is corrected. As the slope of the palpebral apertures and that of the orbital axes change at completely different times during development, and as they are in the opposite vertical direction in adult mongoloids, the two must be independent. The cause for the peculiarities in the eyelids is much more likely to be in the skin itself rather than in the underlying bony configuration.

In the disease known as congenital ectodermal defect, there are numerous anomalies of the epidermis and its appendages because of faulty differentiation of the epiblastic layer. They may arise from incomplete development of the surface ectoderm or its absence in circumscribed areas. The palpebral apertures may be shortened, slope upwards and outwards, and present an appearance amazingly like that seen in mongolism. Some subjects are mentally defective, but most are normal, because the anlage of the nervous system is

distinct from the cutaneous ectoderm before the defect begins (Andrews, 1947).

In dermatomyositis and scleroderma severe skin shrinkage may cause changes in alignment of the palpebral apertures to resemble those seen in mongolism.

In mongolism skin texture is rarely normal, whilst exaggerated flexures and clefts are almost constant. The dermal patterns show many interesting features. Their form is determined before the third month of foetal life (Cummins, 1936).

The surface ectoderm is probably affected very early during development, and disturbances within it may be responsible for the appearances of the palpebral apertures so characteristic of mongolism.

EPICANTHUS

Epicanthus has been stressed by many writers, but there is nothing very unusual in this feature. It is common among European babies, but usually disappears during the early years of growth. The persistence of epicanthus throughout life may be genetically determined due to a pure or irregular dominant gene (Usher, 1935).

Von Ammon (1860) divided epicanthus into three main groups.

1. Epicanthus supraciliaris—the fold arises from the eyebrow.
2. Epicanthus palpebralis—from the skin of the upper lid above the tarsal fold.
3. Epicanthus tarsalis—from the tarsal fold. To these Komoto (1920) added a further type.
4. Epicanthus inversus—from the lower lid, enclosing the medial end of the upper lid in a small bow.

Von Ammon considered that epicanthus appears because the skin of the face develops at a much faster rate than the bones. It is loose in the foetal and infantile stages, but when the bones develop with the aging of the child the epicanthus disappears. Chavasse (1939) stated that its disappearance is due to growth of the face, a deepening of the orbits and an increase between them. These changes are said to depend on the development of the jaws, particularly with the onset and increase of dentition. The redundant tissue becomes less, and its looseness disappears.

Epicanthus palpebralis is the most common type seen in European infants. The same form occurs in mongolism. Although epicanthus is common among mongoloid infants, one cannot accept the statement of Brushfield (1924): "Of all the stigmata of degeneration of the head this is one of the most important, the lower the grade of amentia the more certainly will it be found." The epicanthus is merely a further indication of retarded growth in

mongolism, and with development it almost always disappears. Benda (1946) wrote that he had never seen it beyond twelve years of age. In the present series of adults it was only seen once in an obvious form (Fig. 6).

More commonly in mongolism an abnormal looseness of the skin remains in this region, so that when it is stretched from below, folds similar to epicanthus can be produced. Fig. 7 shows case No. 50 as his usual appearance with epicanthus; but with stretching the folds show prominently (Fig. 8). In mongolism the bridge of the nose generally remains flat and broad, but this feature is rather variable, and some of the mongoloids have well-developed nasal bridges.

THE LID EDGES

Young mongoloids have thin normal lid margins with sharp borders in contact with the eyeballs, and a narrower shelf between this ledge and the lashes. During adolescence the skin often becomes rougher, and this ciliary border may thicken, so that a wider ledge projects between the sharp edge and the lashes. On this skin ledge scales may collect and lead to a secondary conjunctivitis. Increase of subcutaneous fat between the skin folds frequently gives a rolled appearance to the lower lids (Fig. 7).

The eyelashes may be rather short, but are otherwise normal unless disturbed by disease. Trachoma has been the commonest cause of gross irregularities. Alopecia affecting the scalp is moderately common. Sometimes it is almost complete, and the eyelashes may be absent (Case No. 50, Fig. 7).

THE LACRIMAL APPARATUS

All the eyes watered profusely after slit-lamp examination, and tears formed readily when the children cried. There was no evidence of deficiency in tear secretion. The drainage mechanism appeared adequate, and epiphora was seen only when there was excessive tear formation, *e.g.*, in old trachoma.

THE IRIS

The fact that there are peculiarities of the iris in mongolism has been known for many years. Many investigators in describing the widespread stigmata refer to the "speckled iris." Brushfield (1924) reported briefly on the iris appearances in 115 cases. He described two main groups, namely the "mottled or marbelled iris" and the "speckled" iris. He observed that the changes were not obvious in the brown irides. He found that approximately 50 to 60 per cent. had blue or grey irides, about 25 to 30 per cent. had brown irides, and 10 to 15 per cent. had hazel-coloured irides.

In the present series of 67 patients, whose ages ranged from one to 60 years, the following iris colours were observed :—

	Per cent.
Blue or Grey (little stromal pigment)	40
Hazel (moderate stromal pigment)	25
Light Brown (heavy stromal pigment)	25
Dark Brown (dense stromal pigment)	10

The colour of any iris depends on the amount of brown stromal pigment present giving its brown colour by reflected light, and on the amount of light scattering caused by the stroma with the densely pigmented epithelium backing it (producing blue or grey colours).

The stromal pigment is seen four to five months after birth in Europeans, first in the cells on the outer iris surface. It increases in amount up to 8 years of age, and in later life diminishes again (Marin).

When a hazel iris is examined with the slit-lamp much of its green colour disappears, and the iris shows more light-brown. This is because there is much less light scattered from the focused beam than with less regular oblique illumination. The change in colour is well illustrated in the iris in Fig. 13, which appeared yellow-green by oblique illumination and golden-brown with the slit-lamp. The colour of the iris does not appear to be of great significance because its appearance normally varies with age, race, and method of examination.

There are two characteristic changes found in the iris in mongolism :—

1. Poverty of the stromal fibres.
2. Peripheral speckling.

Like all stigmata of this disease, the appearances are not confined to mongolism. They are also found in normal people and in those with other diseases, but their presence in such a high proportion of mongols allows these appearances to be considered definite stigmata of this disease, and they count as supporting evidence in diagnosis.

The Poverty of the Iris Stroma. The peculiar, thin iris stroma has not been described previously as a characteristic of mongolism. Among the 64 patients comprising the present series, it occurred to a considerable degree in 60 (approx. 95 per cent.).

Similar to normal senile thinning it increases with age, but by contrast it is present in the youngest children. The most characteristic region to be affected is the periphery (ciliary zone). Around the pupil, most mongoloid children show almost normal

pigmentation, with well-formed stroma and collarette, but near the junction of the middle and outer thirds of the iris surface the stroma suddenly becomes much thinner, the strands diminish in number and thickness, and become very wavy. The dark posterior pigment epithelium shows plainly from behind (Fig. 13). The peripheral strands resemble minute fibres of fluffy white wool. Some show a fine pink blood-column down the centre. Only the thickly pigmented, dark brown irides fail to show this peripheral thinning (4 cases out of 64).

With increasing age depigmentation occurs together with the disappearance of some of the more central strands. A general thinning of the iris stroma then becomes obvious. Pigment remains only in association with the coarse strands, or where strands are bunched together. The light-brown or hazel iris changes slowly in colour to a dark-grey. With the depigmentation and thinning of the stroma the sphincter muscle shows clearly surrounding the pupil (Figs. 10, 11 and 12).

In one patient, case 65, aged 47, some of the strands were coarse near the pupil, but as they passed peripherally they became very thin. A few had apparently become detached from the main iris layers, and had gained a secondary attachment to the cornea. They passed forward to join the posterior corneal surface just medial to the limbus (Fig. 12).

Sometimes, as the attenuated peripheral fibres disappeared leaving the coarser strands, a scalloped design remained with the dark posterior pigment epithelium showing plainly in the depths (Fig. 11).

When coarse stroma had not been present, as in blue irides, the thinning of the fine strands formed a delicate lace pattern. Each fibre then resembled very fine wool, and the central blood column was frequently seen.

Uncommonly (2 cases, approx. 3 per cent.), stromal atrophy was very pronounced around the pupil as well as at the periphery. The pupil was not significantly altered in shape, but the posterior pigment epithelium showed as a thin, flat layer in association with the sphincter. With the slit-lamp densely pigmented clump-cells were prominent on its surface.

The Speckled Iris. The speckling is associated with the peripheral thinning, but is not dependent upon it. It is sometimes seen in normal people where the thinning appears to be absent. It is then usually not so obvious, and is very uncommon in association with other than blue irides..

In young mongoloids, just beyond the region where the stroma pigment suddenly becomes thinner, the strands tend to bunch at almost regular intervals around a circle concentric with the pupil.

Where these strands run together, pigment collects or the strands remain thicker, thus presenting an appearance of small golden or white splashes.

This speckling was found in 56 patients in the present series (nearly 90 per cent.). Its appearance has been noted by previous observers, and it is considered a characteristic of mongolism. When the eyes are moist it gives a most attractive appearance to shining blue eyes. As atrophy advances the speckling remains much longer than the stromal pigment around the pupil, and in no case had it completely disappeared. It is not seen in the evenly pigmented dark brown irides.

Conclusions concerning the Iris. As the iris changes are found in the youngest mongoloids the appearances suggest a possible hypoplasia of the peripheral parts of the stroma. As the thinning continues throughout life, and in later years is very pronounced, an atrophic process is probably superimposed.

In any iris most of the strands consist of relatively thick-walled blood vessels. In mongolism the vascular system is remarkably hypoplastic. Structural abnormalities of the heart, narrowing of the main trunks, and inadequate, thin peripheral capillaries are very common. The hypoplasia of the iris stroma, with its peripheral thinning and fine woolly strands showing central blood columns, is in keeping with the widespread changes in the whole vascular system.

In normal people the iris becomes thinner with age, and the changes are accelerated with the onset of senility. In many ways adult mongoloids appear to deteriorate more rapidly than normal, and the advancing iris changes are perhaps merely another example of this decline.

In contrast with the stroma, the posterior pigment epithelium of the iris is avascular, develops from a different germ-layer, and is unaffected. It always appeared very deeply pigmented, and by transillumination no thin patches were seen. The ectodermal iris muscles are apparently unaffected, as the pupil reactions are not appreciably altered.

THE PUPILS

The pupils showed no abnormalities in size, position or shape. Their light reflexes (direct and consensual) and near reflexes (accommodation and convergence together) were brisk and appeared normal.

At the first examination many mongoloids may show somewhat enlarged pupils. The dilatation is apparently due to fear of the strange examiner and his instruments. They showed many other evidences of fear, but these disappeared as confidence was gained

by repeated examination, and when they knew they would not be hurt.

With homatropine and cocaine the pupils dilated evenly and to a normal extent. As with normal people, the dilatation was less complete in some of the older patients.

The normality of the pupils is surprising in view of the changes in the iris stroma, but it is understandable when the limits of the hypoplasia are known.

The Interpupillary Distance. Brushfield (1924) found that the average interpupillary distance in 84 mongoloids was 5·2 cm. in males and 5·4 cm. in females. The mean distance between the pupils among unclassified mental defectives was 4 cm. Probably most of the subjects were children.

In the present series the average interpupillary distance of 17 fully grown adult, non-squinting mongoloids was 55 millimetres, with extremes of 52 and 60. These distances are in keeping with those found by Brushfield. These readings are only approximate because the eyes waver, and the method of measurement is a pair of calipers extending from the edge of one pupil to the corresponding point on the other pupil. The eyes are set about 5 millimetres closer than in normal adult Anglo-Saxons, but the general stature and head size of the mongoloids are smaller.

During growth the interpupillary distance and the skull breadth do not extend evenly, and the increase of each does not necessarily occur at the same time. In mongolism the growth of the skull in breadth is much less affected than in other directions. Sometimes the interpupillary distance seems to lag behind the increase in the interparietal diameter, and the eyes then appear set abnormally close together.

LENS OPACITIES

Ormond (1910) was the first to describe the typical lens opacities of mongolism. He examined 28 cases and found lens changes in nineteen. Subsequently (1912) he extended his series to 42 patients, finding 25 with some form of cataract. All his investigations were conducted with oblique illumination, and he observed that some of the opacities were very thin, being invisible if the light were not sufficiently oblique. He described most of the cataracts as a dot variety in lamellar form. Some of his illustrations show Y-shaped sutural opacities, although he did not describe them as being related to these structures. He also found an incomplete variety existing as a single circumscribed opaque mass in one meridian of the lens. He observed that the opacities did not reach to the periphery of the lens. Contrary to the findings in the present investigations, his illustrations show them to be thickest

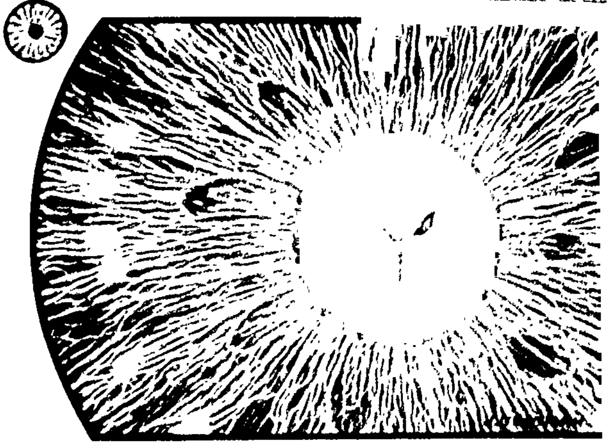


FIG. 10. Iris of mongoloid No. 43, aged 35 years Blue iris showing white speckling, fine stroma, posterior pigment epithelium and sphincter.

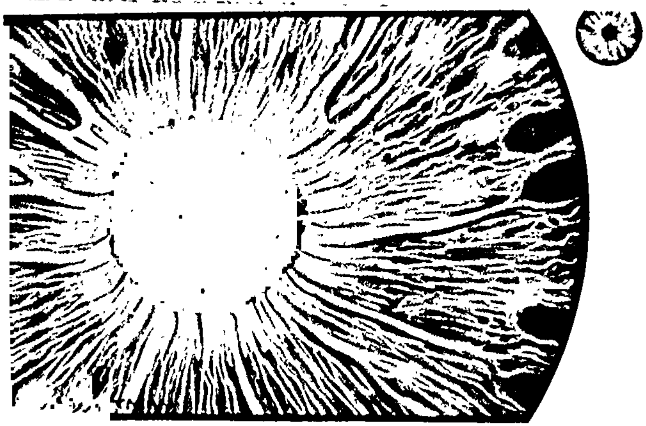


FIG. 11 Iris of mongoloid No. 47, aged 37 years. Thin grey iris showing white speckling, and very pronounced atrophy of stroma at periphery (ciliary region)

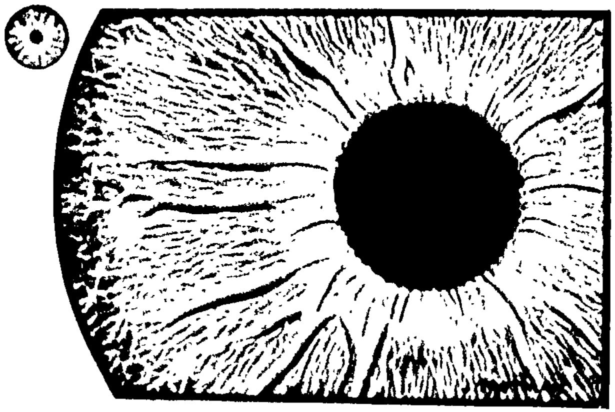


FIG. 12. Iris of mongoloid No 65, aged 47 years. Thin grey iris showing advanced stromal atrophy and thick strands becoming very thin towards the periphery.

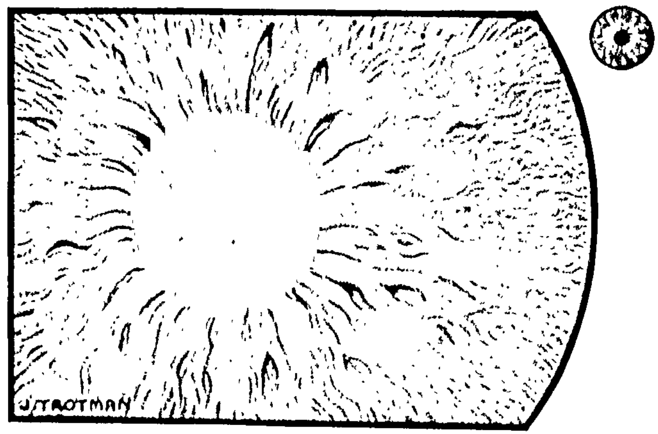


FIG 13. Iris of mongoloid No. 39, aged 32 years. Hazel iris, thickly pigmented around the pupil where the stroma is coarse, showing characteristic thinning of the stroma towards the periphery

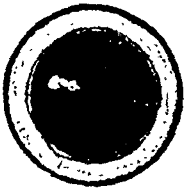


FIG 14*a*.

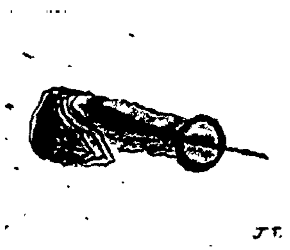


FIG. 14*b*.

FIG. 14*c*.

FIG 15*a*.

FIG 15*b*.

FIG 16*a*

FIG 16*b*.

FIG. 14. Lens of mongoloid No. 54, aged 40 years. (*a*) Appearance with loupe showing flake opacities and small deep arcuate opacity. (*b*) The arcuate opacity as seen by diffuse illumination with the slit-lamp microscope (*c*) Optical section of lens with the slit-lamp, showing the arcuate opacity in the deepest layers of the foetal nucleus and flake opacities in the infantile and adult nuclei.

FIG 15. Lens of mongoloid No. 33, age 26 years. (*a*) Appearance with loupe showing numerous flake opacities and axial stellate cataract. (*b*) Optical section showing stellate splashes in the same layers as the other flakes (infantile and adult nuclei).

FIG. 16. Lens of mongoloid No. 53, aged 40 years. (*a*) Appearance with loupe showing flake and arcuate opacities. (*b*) Appearance with high magnification with the slit-lamp. The arcuate opacities have been reduplicated several times. The peripheral coronary splashes have a pallisade appearance and the small flakes are superficial to the deep arcuate opacities.

FIG. 17c.

FIG. 17b.

FIG. 17a.

FIG 17. Lens of mongoloid No. 32, aged 26 years. (*a*) Appearance with loupe showing Y sutural cataract and peripheral splashes (*b*) Magnified view of Y suture cataract and flakes. (c) Optical section showing Y suture cataract in the deepest layers of the foetal nucleus, with flakes of different colour and size localised to the infantile and adult nuclei.

FIG 18a.

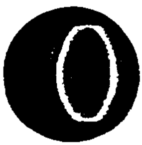


FIG. 18b.

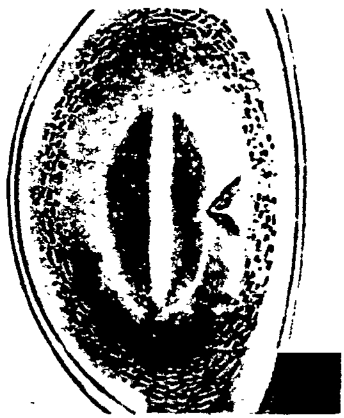


FIG. 18c.

FIG. 18. Lens of mongoloid No. 48 aged 37 years. (*a*) Appearance with loupe showing numerous small blue flakes, especially towards the periphery (*b*) Optical section without magnification showing flakes in distinct bands in the infantile and adult nuclei (c) Optical section with slit-lamp microscope showing different sized flakes thickly spread in the infantile and adult nuclei. The Y suture opacity is only seen with high magnification.

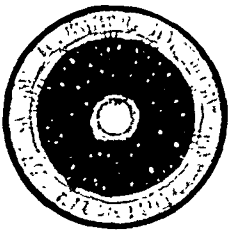


FIG 19a.

FIG. 19d.

FIG. 19b

FIG. 19c.

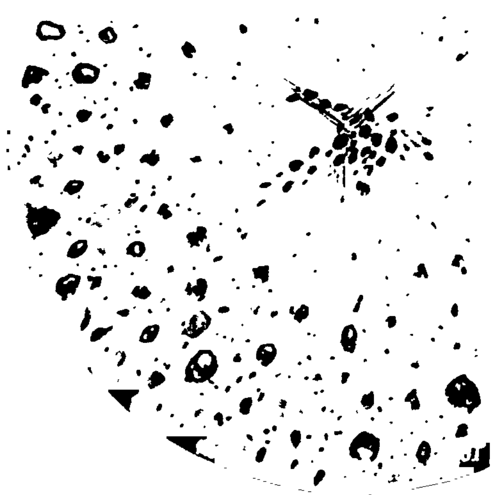


FIG. 19e.

FIG 19. Lens of mongoloid No. 41, aged 32 years (*a*) Appearance with loupe showing small flakes and posterior polar cataract (*b*) Optical section without magnification showing flakes within the adult and infantile nuclei, fine opacities in the foetal Y suture and posterior polar cataract. (*c*) Magnified view of feathery Y suture cataract extending in depth throughout the foetal nucleus. (*d*) Denser opacities in the less regular sutures of the infantile and adult nuclei. (*e*) Magnified appearance of flakes showing different colours and bizarre forms, thickest towards the periphery.

at the axis. From the absence of these opacities in very young mongoloids he concluded that they were of late development.

Van der Scheer (1919) reported 60 cases examined for opacities. He found cataracts in 36 of them and confirmed Ormond's observation of their absence in mongoloids under eight years of age. He divided the opacities into three types:—

1. Punctate, macular and floccular opacities.
2. Snow-flake cataract (cataracta punctata disseminata).
3. Y-shaped opacities, which he recognised as being related to the sutures in the lens of the new-born.

Ormond and Van der Scheer were the only investigators to describe more than a few cases in any series. Jeremy (1921) reported a further case, which probably had bilateral dense lamellar cataracts. Leeper (1912) published a series that is strange in having characters identical in every way with those reported by Ormond (1910). Brushfield (1924) mentioned three cases, but gave no details of the appearances. Ormond and Van der Scheer conducted their examinations without the aid of the slit-lamp. With this instrument and the increased knowledge that had been built up by its use it became possible to extend the observations and more accurately to localise the layers involved.

Koby (1924) examined one patient, and Goulden (1928) reported three more.

The Present Investigation. In all, 52 patients were examined. All were examined with oblique illumination and binocular loupe, (x3) and with their pupils fully dilated. Thirty-one were further examined with a slit-lamp. For the oblique illumination an electric ophthalmoscope was used after removal of the lens head. This could be readily moved in different directions and held so that the light was thrown into the lens almost tangential to its surface. The extreme obliquity was necessary to see the thin flake opacities when they were few in number. If the light was too direct it passed through the flakes, and unless they were relatively numerous they were easily missed.

The mongoloid patients soon lose their fear of the instruments, but one cannot expect their eyes to be held steady for more than a few seconds. With the slit-lamp one has to chase the continually moving eyes, or at times wait for the lens to return to the focused position.

The 31 patients examined with the slit-lamp varied in age from 20 to 51 years. The slit-lamp was not used for children, as it was considered that little extra information would be gained for the greatly increased difficulties. The oldest patient, aged 60 years, was unable to be moved from bed, and some were unsuitable subjects because of trachomatous pannus.

Types of Cataract. The cataracts were found to fall into 4 main groups.

1. Arcuate opacities—commencing during the formation of the foetal nucleus.
2. Sutural opacities—mainly affecting the anterior Y sutures of the foetal nucleus, but occasionally showing in later sutures.
3. Flake opacities—characteristically within the infantile and adult nuclei.
4. Various congenital cataracts with individual differences.

The Arcuate Opacities. The arcuate opacities are the earliest to develop, as they show plainly within the foetal nucleus. The simplest form is seen as a small white arc deeply within the lens (Fig. 14, Case No. 54). Such a cataract appears to have been formed in relation to an abnormal capsulo-pupillary vessel during early foetal life.

The capsulo-pupillary vessels begin to regress during the fourth foetal month, and their disappearance is complete at birth or a little later (Mann, 1937).

The smallest arcuate opacities are quite narrow and relatively thin. They arch around the equator of the early layers of the foetal nucleus, and extend radially anteriorly and posteriorly. They may be practically flat-surfaced, or have a central rib—probably from the remains of the vessel. They then appear like tiny curved white leaves deep in the lens. Such appearances suggest a cause that has acted for a short time but caused no permanent damage to the growing cells.

Sometimes the injury is more severe so that all the lens fibres laid down in the affected region become opaque. A large, white sector-shaped opacity then develops extending from the foetal nucleus right out to the periphery. In these cases no coloboma of the lens was found in the affected part, but considerable lenticular astigmatism was evident.

If the disturbance that causes an arcuate opacity were to act over the whole of the circumference of the foetal lens instead of being localised to one sector, a lamellar (zonular) cataract would form. The lens cells might recover and lay down clear lens fibres again, or they might continue to produce opaque fibres showing as a completely white lens.

At other times the developing cells in the affected region appear to recover from the initial disturbance and lay down clear lens fibres, but apparently they do so with reduced vitality. Some future upset, possibly a metabolic disturbance or an intercurrent illness, causes the production of opaque fibres again for a short time, with recovery and clear fibres again later. In this way the original opacity may be reduplicated several times within the lens

at different depths between the foetal nucleus and the surface (Fig. 16, Case No. 53).

One arcuate opacity was found in a child of 11 years. It was very dense and appeared likely to have been present at birth. These cataracts are the earliest type to be seen in mongolism, and could be expected to be found at any age. In the present series of 52 cases (103 eyes) they were detected in 8 patients (11 eyes).

The Sutural Opacities. The Y sutures of the foetal nucleus are recognisable at 8·5 weeks of foetal development (35 mm.), and this pattern persists until just before birth, when the adolescent (infantile) nucleus begins to form with 4 rays instead of three (Mann, 1928).

In the present series 14 patients had opacities of the Y sutures. In practically all, the changes were bilateral. The anterior upright Y was always clearly identifiable (Fig. 17, Case No. 32), but the posterior inverted Y was always less distinct. The limbs of the anterior Y always showed plainly, but on the very few occasions when an opacity was present in the position of the posterior Y it showed as a faint irregular blur.

The youngest patient to show a sutural opacity was aged 11 years. Two children aged 13 and one aged 17 showed similar opacities. In these young patients the sutural opacities were extremely delicate and would have been missed had a special search not been made for them. For the most part, similar cataracts were quite obvious in adults. They therefore gave the appearance of developing within the foetal sutures some years after the sutures were laid down, and of thickening very slowly to become obvious only many years later.

It is to be expected that slit-lamp examination of young children would reveal some of early appearance, because in some of the adults their presence was not recognised with the loupe, and only found with the slit-lamp (Fig. 18, Case No. 48). With the loupe, when these opacities are very fine they appear like tiny strands of cobweb. When denser they are blue, and the little Y is easily seen. The slit-lamp shows that they extend for varying depths within the foetal nucleus. They are usually linear in form (Fig. 17), but sometimes they have a feathery appearance as the narrow beam moves across (Figs. 18 and 19). A few showed the more superficial parts like strings of small green beads. (Fig. 19).

Only four cases showed definite opacities of more superficial sutures. They usually appeared as very fine grey lines extending irregularly from the axis at varying depths within the infantile nucleus.

Flake Opacities. Vogt (1921) described wreath-shaped or coronary cataracts and found them in 25 per cent. of normal

adults. In the present series of 52 patients, opacities of this type were found in forty-five. If the patients under 14 years of age are excluded, flake opacities were found in 43 out of 47 (92 per cent.).

Examination with oblique illumination and binocular loupe shows two types of flakes. The commonest form consists of fine blue or smoky-grey minute flakes (snow-flake cataract of Van der Scheer). In young mongoloids they are very sparse. The pupils must then be dilated, as they are commonest somewhat internal to the equator, and the axial region remains free until they become relatively numerous. They are readily seen in most adults.

The other form of flake cataract is found as equatorial, white or light-brown radial spokes. They resemble the more usual coronary cataracts, but they are mostly lanceolate in outline and rarely club-shaped. Often they arch around the equator of the affected nucleus. Sometimes they are closely packed and have a palisade appearance involving certain sectors of the lens (Fig. 16). The peripheral splashes rarely extend towards the axis, but sometimes they do so, particularly in the posterior layers.

The small flakes and peripheral splashes are usually associated, but in very varying proportions. Arcuate opacities, sutural cataracts and flake opacities may be seen within the same lens.

With the slit-lamp the flake opacities are localised mainly within the infantile and adult nuclei. Very occasionally they extend more deeply and may be seen with the Y-shaped opacities within the foetal nucleus. Rather more often they may be found superficially, gradually thinning as the outer layers of the cortex are reached.

When a narrow beam from a slit-lamp is shone into a typically affected lens, and the result observed with the naked eyes, the affected zones stand out very prominently as anterior and posterior bands within the lens. A lamellar appearance is then presented (Figs. 15, 18 and 19).

With the binocular microscope, the flake opacities are seen to be very much more numerous than previously expected, and to assume extremely variable forms. Many appear like tiny blue or white snowflakes varying in size up to about one quarter of a millimetre. They are often thicker at the edges, and some appear as bizarre rings. The thicker opacities are more opaque, suggesting small drops of paint (Fig. 19).

Dust-like particles are very numerous. Possibly fine crystals are also present, because occasionally the beam is reflected as a tiny, brilliant, red or green light like a minute spangle.

The equatorial splashes are larger, but localised within the same nuclear layers. Infrequently they may extend from the axis, giving a stellate appearance to the cataract (Fig. 15).

The colour of the flake opacities may be blue, grey, green, white

or light-brown. The colour probably depends on the different ways that the light is dispersed. By their appearances they may be classed as forms of coronary cataract.

These opacities are as a rule sharply localised within the infantile and adult nuclei, rarely being found deeper or more superficially. The deeper layers of the affected bands show no denser collections and no larger particles than the later-formed more superficial layers.

As the flakes are rarely found near the lens surface, irrespective of age, it appears that they gradually form after the lens fibres are laid down, but once they have reached their distinctive thickness and shape, little further change occurs.

In their investigation the youngest patient showing them was aged 9 years, but the children were not examined with the slit-lamp. As the flakes are occasionally seen within the foetal nucleus of adults, some infants would probably show their presence by slit-lamp examination. Although they are very sparse in children they are almost always seen in adults. They bear no direct relationship to age. The oldest patient, Case No. 67, aged 60, showed few of them and they were most numerous in Case No. 49, aged 38 years (see Table No. III).

Hess (1893) showed that the anatomical basis for coronary cataract is lacunae between the lens fibres. The spaces are filled with homogeneous or finely granular coagula that stain deeply with haematoxylin. According to Vogt the opacities consist of fluid, and the form of the opacity depends upon its location in the concentric zones, *i.e.*, if the vacuoles lie peripherally, club-shaped opacities result, whilst axially located vacuoles cause disc or ring shapes. Within the fluid there may be cellular débris, crystals, protein or lipoid particles. The thickness and fluid or particulate contents determine their optical effects upon the light beam and their different colours.

The flake and sutural opacities are probably of the same nature but in different location, whereas the arcuate opacities are of another character. It is important to emphasise that the appearances of the flakes, being purely optical phenomena, give no indication of their underlying cause.

The presence of large numbers of flakes is consistent with adequate vision, for owing to their thinness they obstruct little light. When they were very numerous the fundus could not be seen with an electric ophthalmoscope, and visual acuity must have been considerably reduced. The central opacities have a very unfavourable affect on vision.

As the older patients require relatively little vision for their interests, extremely few of them need any surgical attention. Even

those with dense central cataracts are able to manage in limited surroundings.

Uncommon Congenital Cataracts. The presence of mongolism does not preclude the formation of better-known types of congenital cataract. Five eyes were thus affected in three patients.

Case No. 16, aged 11 years, had a typical dense right disc-shaped cataract. Thick bilateral lamellar cataracts were present in Case No. 56, aged 42 years. In childhood his lenses had been needled, but the results were poor. Typical posterior polar cataracts from the imprint of the hyaloid artery were found in each eye of Case No. 51, aged 39 years (Fig. 19).

These cataracts may be directly associated with mongolism or due to an independent cause. Some congenital cataracts can be genetically determined, their presence in a mongoloid being purely fortuitous. It is not known whether any disease can be responsible for both mongolism and congenital cataract (*e.g.*, rubella).

Similar Cataracts in Other Diseases. The flake and dust opacities are usually considered to be similar to the cataracts occurring in other diseases (so-called endocrine cataract). Suggestive similarities are found in many cases with myopathy (*e.g.*, myotonia atrophica) but the myotonic cataracts have some differences.

Several patients with myotonia atrophica were examined with the slit-lamp. In every case the cortex was involved more than the deeper layers. Compared with mongolism these appearances suggest that the opacities form more quickly after the fibres are laid down. The faster progress in myotonia is also shown in the usually rapid advance to mature total cataract. Many myotonics require operation to restore vision, as the loss is so severe. Few, if any, mongoloids require surgery, as most of the opacities progress little.

Twelve cretins aged between 26 and 61 years were examined. Most of these patients were receiving thyroid, but their clinical appearances were typical of congenital sporadic cretins. Arcuate or sutural opacities were absent. In eight cretins flake opacities were seen with the slit-lamp, but they were much less numerous than those seen in mongoloids of similar age. The flakes were visible with the loupe in four cretins. The most frequent site for the flakes was the adult nucleus, but sometimes fine specks were seen in the deeper parts of the cortex. Eight of the cretins showed a very marked zone of disjunction between the cortex and the adult nucleus reminiscent of a very thin sheet of mica. This appearance was not seen in mongolism.

Pituitary infantilism may cause lens opacities, and one patient was examined. She was aged 29 years, but had the appearance of a girl about fourteen. Unfortunately she had only one eye, the

other having been lost from an injury. The opacities were minute flecks just visible with reflected light from an electric ophthalmoscope. With the slit-lamp numerous very fine particules were seen in the deepest layers of the cortex and outer zones of the adult nucleus. Scattered flecks extended forwards into the more superficial parts of the cortex. A few peripheral coronary splashes were present. The appearances were not like those seen in any mongoloid, but more like those found in some of the cretins. A further resemblance was the presence of a band of white specks just outside the embryonic nucleus. These central specks were seen in three of the cretins, but in only one of the mongoloids, and he was reported to have suffered from rickets in infancy. The flecks were more numerous than in the anterior axial embryonic cataract (Vogt).

These lens appearances may be important in view of the suggestion by Benda that mongolism is due to a hypopituitarism. This isolated observation does not support such a view, but it would be interesting to investigate the lenses of more patients with pituitary deficiency diseases.

Conclusions concerning the Cataract. The lens is an exceptional organ in that none of the cells formed during its development is normally destroyed or replaced. As it is a clear structure, any opacity occurring within it from the earliest weeks of the embryo to the last days of post-natal life can be localised in time. The earliest cells are at the centre, and the later-formed fibres are superimposed like the layers of an onion. The time at which the different layers form is known from histological and slit-lamp examinations.

The developing lens separates from the surface ectoderm about the 10 mm. stage (4 weeks+) (Mann, 1937), and the primary lens fibres begin to form a few days later. The earliest fibres remain as a clear zone at the centre of the lens.

A disturbance of the formation of the primary lens fibres is said to cause a disc-shaped cataract (Collins, 1908). One patient (Case No. 16, aged 11 years) showed a typical disc-shaped cataract of his left lens. This might indicate abnormal development at the very early stage of 5 to 7 weeks. Unfortunately our knowledge of disc-shaped cataract is not precise, and as this type of cataract was seen in only one eye in the present series, its occurrence with mongolism might have been fortuitous.

The most distinctive cataracts in mongolism are the arcuate opacities. They were seen in one-sixth of the patients investigated. They are extremely rare in normal people or in those with other diseases. Similar opacities have been reported in association with coloboma iridis where an abnormal capsulo-pupillary vessel caused

extensive developmental defects (Mann, 1934). In mongolism these associated disturbances of other parts of the eye are lacking. The deepest layers of the arcuate opacities are found encircling the early secondary lens fibres at the same level as the most internal parts of the Y sutures. This corresponds with the 35 mm. stage (8·5 weeks) of foetal life. At this time the vascular capsule of the lens is well formed, and presumably the developing lens fibres depend upon the vessels for their nutrition. A few weeks later the vascular capsule begins to regress, and the lens then obtains its nutrition by fluid exchange from more distant sources. This change allows light rays to be unimpeded in their passage to the retina.

Abnormal vessels during development would be most likely to cause defects in lens structure during the period when they are supplying the lens fibres directly, and the fibres most susceptible to damage would be those dividing at that time. The arcuate opacities are examples of this disturbance being caused by the presence of abnormal capsulo-pupillary vessels. They provide proof that in mongolism the peripheral vessels may show abnormalities as early as 8·5 weeks. This is in keeping with developmental defects seen in other parts of the mongoloid vascular system, *e.g.*, heart. The arcuate lens opacities are different from the other distinctive cataracts found in mongolism, as they are probably due to opaque lens fibres and not to opacities between the fibres.

In mongolism the sutural and flake cataracts are much more common than the arcuate opacities, but they are also found in normal people and in those with other diseases. Their incidence is unusually high in mongolism. The peculiar shapes of the sutural and flake cataracts are due to fluid and débris between the lens fibres. As their appearances are purely due to their optical properties, there is no justification for assuming that they are caused by the same factors that produce similar appearances in other diseases. They are often thought to be caused by those endocrine disturbances which are so extensive in mongolism. The cause is almost certainly a metabolic peculiarity, but its nature is unknown. A satisfactory explanation will be provided when more is known of the biochemistry and physiology of the lens. Until then the account must be purely descriptive.

THE INTRA-OCULAR FLUIDS

By clinical examination no abnormalities were detected in the aqueous. The intra-ocular pressure always appeared normal to palpation, and no evidence of glaucoma was seen. The vitreous was always free of developmental structures as observed with the

ophthalmoscope. The only pathological changes were those associated with myopia, when vitreous floaters were commonly seen.

THE FUNDUS OCULI

The optic disc varied no more than would be expected in the examination of a random sample of the general population. Many of the discs appeared pronouncedly pink, like those commonly seen in children. Possibly it was this appearance that gave some of the older writers (Oliver, 1891) the impression that neuro-retinitis was common, but there is nothing to support such an interpretation.

Small congenital crescents and pigmented arcs were fairly common, but von Szily has shown that such conditions occur in 25 per cent. of normal people.

Typical myopic crescents were found in those with high myopia. They were associated with the usual fundus changes, *i.e.*, thinning of the choroid, large choroidal vessels clearly seen, patches of atrophy and pigmentation.

The macula was carefully examined when it was not obscured by lens opacities. The foveal reflex was constantly present, and ophthalmoscopic appearances always suggested that it had differentiated anatomically.

Apart from fundus degenerations associated with myopia, anomalies were rare. Case No. 29, an extremely low-grade ament, showed an incomplete choroido-retinal coloboma extending downwards and outwards from the right optic disc, which had an eccentric pit in the same direction. Case No. 67, aged 60 years, had typical gyrate atrophy associated with high myopia. The clear-cut, atrophic, circular patches extended around both discs and maculae. Fixation had been lost with the right eye.

VISUAL ACUITY

Very few mongoloids can be tested for visual acuity by the usual clinical methods. Most of them never learn to read, although many more could be taught if special attention were given to their slow development. Only 5 of the 67 patients could read Snellen's Test Chart (see Table No. II).

The best visual acuity recorded was 6/12 right and left eyes in a male, aged 34 years, I.Q.34, who had only a few lens flakes. By retinoscopy he had almost no refractive error. For reading he brought the type to a distance of about 6 inches from his eyes, to gain the benefit of larger retinal images, and then read J.1. The remaining four patients had less clear vision, which improved little with attempted correction after refraction. Subjective testing was

impossible, because they could not grasp the significance of "better or worse" when lenses were changed.

The attainment of 6/6 vision is a conditioned reflex which depends on appropriate stimulation and reinforcement (Chavasse, 1939). The development of such a conditioned reflex is subject to many hazards in mongolism. Some of the commonest may be mentioned. The reception of stimuli by the appropriate sensory end organs at the maculae may be disturbed by congenital lens opacities (arcuate, lamellar, posterior polar), or the retinal image may not be clearly focused, producing insufficiently defined stimuli (congenital myopia, astigmatism, nystagmus). Sufficient anatomical development, awareness and docility are further requirements for the development of any conditioned reflex (Pavlov). All are variable and in some cases inadequate in mongolism. In later life the onset of strabismus, developmental lens opacities, myopic degeneration and trachomatous pannus cause further visual loss.

The lower grades of aments will be found to have very poor visual acuity. Some can only fixate objects momentarily, and ocular nystagmus is pronounced. Others move their eyes from place to place with apparent inability to concentrate on any particular object. The higher grades will develop interest and much better visual acuity, but with increasing age the risks are multiplied by developing lens opacities and high myopia.

The visual acuity of mongoloids is seldom good, but their requirements are so limited in their homes and institutions that, even with grossly reduced vision due to dense lens opacities, very few require special attention for these defects. For those who are to receive special schooling a full ophthalmological examination should be conducted early, to determine the presence of lens opacities or to correct any refractive error (particularly myopia).

COLOUR VISION

Nine patients were found to have sufficient intelligence and lenses clear enough to be tested for ordinary colour vision. No scientific methods were used, but a series of 20 pairs of coloured wools were presented for naming and matching. Pastels and common confusion shades were included. In no case was any significant defect suspected. Sometimes the wrong wools would be chosen in an attempt at quickness, but on their refusal the right colour would be found. For those who could name the colour the correct word was always given.

The colour vision of mongoloids is clinically normal in those who have sufficient mental development for colour to be of significance.

REFRACTIVE CONDITION

With mydriasis by homatropine and cocaine, retinoscopy was performed on 35 patients ranging in age from 5 to 60 years. An electric retinoscope was used, together with spherical and cylindrical lenses in a trial frame. The power and axis of any astigmatic correction could then be recorded as accurately as possible. The results are summarised in Table No. I. The astigmatism could not always be determined very accurately owing to irregularity from lens opacities, trachomatous pannus, or head and eye movements. In the table these cases are indicated by the " ? "

The 35 cases may be divided into 2 groups :—

1. Those with physiological variations from emmetropia.
2. Those with high myopia.

Twenty-two patients (approximately two-thirds) showed refractive errors which may be considered as physiological variations of emmetropia. As in any similar series of normal people, there is a tendency for the refractive errors to vary little from emmetropia. Astigmatism was not very high, and its axes were usually symmetrical in the two eyes. Sometimes arcuate opacities caused the astigmatism to be less regular. In this group the vitreous and fundi were normal.

Thirteen patients (approximately one-third) were high myopes. By focusing the equators and the posterior poles of the fundi the myopic refraction was seen to be mainly axial. Vitreous floaters, choroido-retinal thinning and degeneration, and bilateral convergent strabismus were all common findings in this group, but retinal detachment was not seen. The myopia is no different from that in the general population, but its incidence is very much greater. The simple, non-progressive, uncomplicated myopia must always be differentiated from the sinister type with its fundus degenerations and visual catastrophes. It is the latter severe myopia which is found in such a large number of mongoloids.

The aetiology of high myopia is still uncertain. Its frequency among some races (Jews, Japanese), its repeated appearance in some families, and its association with some hereditary diseases (non-progressive night blindness) all indicate its genetic background. But its inheritance is not simple, and has been confused by the failure to separate the different types. Possibly its occurrence is conditioned by multiple factors. The effect of environment in foetal life is not known. The very high incidence of severe myopia in mongolism raises many interesting speculations, but difficulties immediately arise because of our profound ignorance concerning myopia in general.

TABLE I—*Showing the refractive errors determined objectively in 35 patients with Mongolism*

Case No.	Age	Right Eye Sph.	Right Eye Cyl.	Right Eye Axis	Left Eye Sph.	Left Eye Cyl.	Left Eye Axis	Remarks
10	7	+1·0	?	—	+1·0	?	—	—
13	9	+1·5	?	—	+1·5	?	—	—
14	10	+2·5	+2·5	60	+2·5	+2·0	130	—
15	10	−1·5	+3·5	80	0	+3·0	100	—
16	11	CAT	—	—	0	−2·0	135	Irregular reflexes, arcuate opacity (lens) 2 o'clock
19	12	+4	irreg	—	+4	irreg	—	Fine corneal opacities
21	13	+1·0	+0·5	180	+1·0	+0·5	180	—
22	13	+6·0	+1·0	90	+6·0	+1·5	100	—
23	13	+7·0	?	—	+7·0	?	—	R.C.C.S. with slight R. abduction weakness
26	20	+1·0	?	—	+1·0	?	—	—
28	25	+0·75	+1·75	75	+1·25	+2·25	115	—
37	30	+1·0	+1·75	20	+1·0	+2·0	140	—
39	32	+1·0	+2·25	30	—	—	—	L. corneal nebulae
41	32	+1·25	+0·5	90	+0·75	+1·0	50	—
43	35	+2·5	+1·25	80	+2·5	+1·0	140	L.C.C.S. 45° amblyopic L.
45	35	+1·0	+0·25	90	+0·5	+0·25	90	—
48	37	+0·5	+3·5	45	0	+3·5	135	—
50	39	+0·5	+1·25	90	+0·75	+1·0	90	Alternating C.C.S. 20°
54	40	+0·75	+1·75	45	+1·5	0	—	—
58	43	+1·5	+2·75	35	+0·75	+2·0	180	L. arcuate lens opacity 2 o'clock, intermittent accommodative squint
65	47	+2·25	+1·5	90	+2·25	+1·75	90	L.C.C.S. about 15°
66	51	−4·5	−1·0	90	—	—	—	Old injury left eye
		HIGH MYOPES						
9	5	−2·0	?	—	−2·0	?	—	High myope in view of age. R. myopic cresent. Frequent rolling twitches
24	14	−15·0	?	—	−15·0	?	—	Typical myopic fundi without atrophy
25	17	−10·0	?	—	−20·0	?	—	Myopic cresents, thinned choroid. Ocular nystagmus. L. converg. squint
31	26	−10·0	−2·0	135	−10·0	−2·0	45	Large myopic crescents, small patches of atrophy
32	26	−8	?	—	−6	?	—	—
34	27	−20	—	—	−20	—	—	Bilateral convergent squint
35	27	−8	—	—	−10	—	—	Typical myopic fundi without extensive atrophy. Trachomatous pannus R. & L.
36	27	−12	—	—	−5	—	—	Bilateral convergent squint with abduction weakness R. & L.
40	32	−15	—	—	−10	—	—	L.C.C.S. about 20°. Wearing undercorrecting glasses
52	40	−15	—	—	−8	—	—	Bilateral convergent squint. Myopic crescents
57	42	−10	—	—	−8	—	—	—
61	44	−20	—	—	−15	—	—	Bilateral convergent squint with severe abduction weakness. Fundus changes
67	60	−12	—	—	−11	—	—	Bilateral convergent squint. Gyrate atrophy R. & L.

TABLE II

Showing the visual acuity and refractive errors of 5 mongoloids capable of reading Snellen's test charts

Case No.	Age	I.Q.	Unaided			Refraction						With Glasses	
			V.R.	V.L.	Near	R. Sph.	R. Cyl.	Axis	L. Sph.	L. Cyl.	Axis	V.R	V.L
37	30	73	6/24	6/18–	J.1 10″	–1·0	+2·0	20	–2·0	+2·0	140	6/12–	6/12–
45	35	34	6/12	6/12	J.1 6″	+0·5	+0·25	90	0	+0·25	90	6/9–	6/9 –
48	37	52	6/36	6/36	J.2 10″	0	+2·5	45	0	+2·5	135	6/24	6/24
54	40	41	6/36	6/36	J.2 10″	+0·75	+1·75	45	+1·5	0	—	6/24	6/24
66	51	34	6/60	—	J.1. 12″	–4·5	–1·0	90	Corneal Nebula			6/60	—

The evidence indicates that, in the main, the refractive conditions of the eyes in mongolism are determined by the same factors which influence them in normal people. The genetic background is probably important, but in some subjects the relationship between myopia and other mongoloid changes is obscure.

Mongolism is a disease in which there is great retardation of growth of many parts of the body. In some organs (*e.g.*, limbs) genetic factors determining size appear to be unable to produce their characteristic effects in the presence of mongolism. In the eyes, however, myopia is associated with excessive growth. The other organ that is characteristically large in mongolism is the tongue.

NYSTAGMUS

Nystagmus occurring in mongolism was recorded in 1899 by Sutherland and subsequently by numerous writers—Muir (1903), 5 in 26 cases; Ormond (1912), 5 in 42 cases; Brushfield (1924), "seldom." They made no attempt to determine its cause or to describe its different types, but merely noted its presence.

When a normal person attempts to move his eyes beyond the limits of the field of normal fixation, the ocular musculature is attempting to cause the eyes to depart beyond their normal excursions. The eyes tend to drift back from these abnormal positions into which they have been forced by the cortical demands. As the

TABLE III—*Showing the types of cataract found in 52 mongoloids from aged 5 to 60 years*

Case No.	9	10	11	13	14	15	16	17	18	19	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37
Age of Patient	5	9	9	9	10	10	11	11	11	11	13	13	13	14	17	20	22	25	25	25	26	26	26	27	27	27	30
Type of Examination ...	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	S	L	S	L	S	S	S	S	S	L	S	S
Arcuate opacities ...	0	0	0	0	0	0	0	2	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2	0	2	0
Y sutural opacities ...	0	0	0	0	0	0	0	0	0	1	0	1	1	0	1	0	2	0	0	0	0	2	0	0	2	2	0
Other sutural opacities	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Scattered flakes & dots	0	0	0	1	1	0	2	0	1	1	1	1	1	1	2	1	1	1	0	0	1	1	3	2	1	2	2
Peripheral splashes ...	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	1	2	1	0	0	1	1	1	2	2	1	1
Central radiating spokes	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0

Case No.	38	39	40	41	42	43	44	45	47	48	49	50	51	52	53	54	55	57	59	60	61	64	65	66	67
Age of Patient	30	32	32	32	34	35	35	35	37	37	38	39	39	40	40	40	41	42	43	44	44	46	47	51	60
Type of Examination ...	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	L	S	S	S	S	L	S	S	L
Arcuate opacities ...	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	2	0	0	2	0	2	0	0	0	0
Y sutural opacities ...	1	0	0	1	3	1	0	0	0	1	1	0	2	0	0	0	0	0	0	0	0	3	0	0	0
Other sutural opacities	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Scattered flakes & dots	1	1	1	2	3	3	2	1	3	2	4	1	2	1	2	1	1	1	1	3	1	3	2	2	1
Peripheral splashes ...	3	0	1	1	1	1	1	1	1	2	1	2	2	4	3	2	2	0	0	3	3	1	2	2	1
Central radiating spokes	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	3	0	1	1	0	0

Examination :— L = loupe. S = loupe & slit-lamp.

1 = few flakes or thin lines. 2 = moderate number. 3 = numerous. 4 = extremely numerous or thick.

drift occurs, it is quickly corrected by pyramidal mechanisms. The drift and check cause a form of nystagmus. This type can be elicited in 50 per cent. of normal persons on extreme forcible deviation of the eyes to one side or the other (Chavasse). It is more easily produced if there are any physical handicaps, or when the person is fatigued. If strabismus is present, nystagmus is often seen when we lead the eyes in the direction against the squint (in the direction of action of the weakened muscle). Many mongoloids do not use their lateral recti as much as normal people, the extreme examples being seen in the common bilateral convergent strabismus associated with uncorrected high myopia.

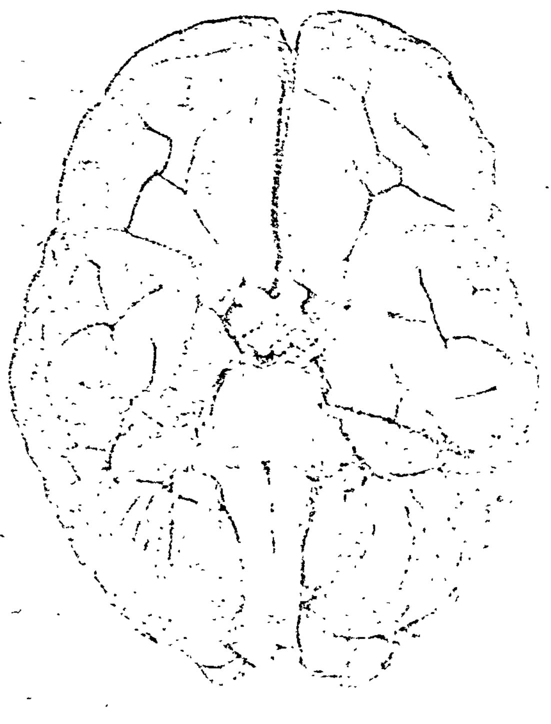


FIG. 20.

Brain of mongoloid No. 72, aged 27 years Showing simplification of gyri, small pons, brain-stem and cerebellum

Owing to the frequency of strabismus, obliquity of the palpebral apertures, and lack of keen interest in their surroundings, this so-called pseudo-nystagmus can be found very commonly in mongolism. The excursions are somewhat more pronounced than in normal people, so that this nystagmus may receive unwarranted attention unless one is aware of its nature.

A feature of mongoloid brains that was noted as early as 1890 by Wilmarth, and subsequently by many observers, is the smallness of the brain-stem and cerebellum (Fig. 20). Sometimes these structures may be only one half the normal size, and on section show considerable cellular irregularity and demyelination.

In view of these changes, nystagmus should be an almost constant feature, but this is not so. In the present series of 67 patients, if one ignores the very brief nystagmus produced on lateral version, which is so common in normal people, then most of them have steady eyes in all directions. After eliminating those with strabismus as a cause of nystagmus when the direction of gaze is led against the weakened muscle, only 9 cases remain. Of these, seven are explicable on the basis of peripheral causes (retinal or ocular nystagmus). They may be subdivided according to the probable cause of their ocular nystagmus as follows :—

1. Lens opacities—5 cases.
2. Maculae at fault, high myopia—2 cases.

In mongolism the commonest causes of nystagmus (and of strabismus) are lens opacities and high myopia. The cataracts prevent clear images falling on the maculae. Uncorrected high myopia results in unfocused images. These may fall on maculae further disturbed by choroido-retinal thinning.

These defects interfere with the fixation reflex, so that control of eye posture *via* afferents from the maculae to the occipital cortices is eliminated, and a pendular type of nystagmus occurs. The searching movements may be constant, or increased by attempted fixation. If fixation can be brought about (*e.g.*, small bright light) the nystagmus diminishes.

The remaining two patients are very low-grade aments, and probably have considerable aplasia or degeneration of the central nervous system. Both have nystagmus constantly in all positions (appendix No. 1). Ophthalmoscopically they have clear ocular media, and the maculae appear to have differentiated anatomically. They were the only subjects with nystagmus apparently due to central causes.

Therefore pronounced nystagmus in mongolism is not commonly due to causes within the central nervous system, but is usually due to ocular defects of which the most frequent are lens opacities and high myopia.

STRABISMUS

The frequent occurrence of strabismus has been noted by almost all writers on mongolism. They agree that the squint is always convergent, but very wide differences of opinion exist concerning its frequency. In 1899 Sutherland reported: "Nystagmus and squinting are often present during the first six months, but pass off as the infant grows." Ormond (1912) found 9 cases among 24 patients examined (21·4 per cent.). Brushfield (1924) said: "Every mongol examined has exhibited this in more or less degree without exception." Most publications on mongolism are written by physicians who apparently formed their opinions purely from the appearance of the eyes in relation to the nose and palpebral apertures.

The bridge of the nose is often wide and flattened in mongolism, and many babies or infants have epicanthal folds. When such a patient looks slightly to one side the cornea turned towards the nose partly disappears, so that the eye seems to be turned inwards much more than its fellow is turned outwards. A squint may be thought to be present when it is not. In any ophthalmic department children are frequently seen who have been brought along under this misapprehension. Similarly, marked obliquity of the palpebral apertures may cause deception.

The presence of strabismus can only be diagnosed when the visual axes are shown to be out of parallel alignment, and the necessary tests are not always easy to perform in very young or retarded children.

In the present investigations the cover test was used whenever possible. This was difficult in many cases because the patient would fixate any object only momentarily, and when the cover was moved the eyes would not be held steady. The more intelligent mongoloids co-operated sufficiently, but in many, reliance had to be placed upon the position of each corneal reflex.

Normal Binocular Vision. The physiology of binocular vision and its perversions leading to strabismus have undergone great advancement since most articles on mongolism were written. The development of binocular function has been admirably described by Chavasse (1939). In considering strabismus in mongolism a short review is desirable.

The attainment of fully developed human binocular vision is a complex process which is not normally achieved until the child is about 6 years old. The underlying anatomical requirements are not completed until several years after birth. Functional fulfilment depends on the development of a number of reflexes, some of which are innate, whereas others have to be conditioned by use. Chavasse described how, during evolution, the two eyes became locked by afferents from *receptors outside the eyes.* The primitive labyrinths were particularly concerned in the control of this early "compensatory reflex." The eyes moved conjugately, but did not have to follow the head slavishly in all its movements. To this coarse control was later added a fine adjustment from afferents arising in the retinae and so visual in nature—"oriental fixation." Later the eyes were able to make disjunctive movements for convergence, increasing the benefits of binocular fixation in relation to objects moving closer to the head.

The human primitive "compensatory reflex" is of such phylogenetic age that it has become unconditionally fixed and is present at birth. The relatively more recent oriental fixation and vergence reflexes are only rudimentary at birth, and if they are not used they are quickly lost. Normally these reflexes are not fully established to resemble unconditioned fixity until the child is aged about 5 years. In young babies apparently aimless eye movements are frequent, but even these "aimless" movements occur only over a restricted range. Horizontal divergence is limited to the position of rest, convergence to about 35 degrees, and vertical deviation is practically never seen. With anatomical completion of the visual pathways and increasing visual awareness, the rewards for convergence are quickly appreciated. The regarded object appears larger and stereoscopically isolated. The convergence reflex is reinforced, and develops rapidly. These reflexes, however, do not lead to increased definition. In addition, a further series of reflexes develops associated with the slower forming accommodation process.

The accommodation reflexes are three in number (Chavasse):—

1. The primitive accommodation–convergence reflex, *via* the occipital cortex. A blurred or double image elicits convergence and accommodation in fixed relationship.
2. The more recent harmonic accommodation-convergence reflex *via* the occipital cortex. There is a physiological range of elasticity between the amount of convergence and accommodation to allow appropriate adjustments to be made.
3. The "voluntary" control from the frontal cortex *via* the pyramidal system. There is no control over individual muscles, so that accommodation and convergence cannot be separately reinforced.

Convergence develops much more rapidly than accommodation in the early months of perception, but by the time the child is five to six years old the two have become fully co-ordinated.

Binocular Function in Mongolism. In mongolism reflex development is greatly retarded, and the visual mechanisms show considerable differences from normal. As has been mentioned previously, the exclusion of suitable retinal impulses sometimes prevents the development of the fixation reflex, and searching or ocular nystagmus ensues.

Among any group of mongoloids a conspicuous feature is the number who retain the infantile habit of converging spontaneously and irregularly. During ophthalmoscopic examination they often attempt to focus the light, and in so doing both eyes undergo extreme convergence. The same phenomenon occurs frequently during refraction from attempts to look at the spectacle-frame. When they follow an object approaching the nose, convergence may be excessive and then adjusted. Sometimes one eye converges more than the other, and is then brought back into alignment.

Types of Strabismus in Mongolism. Among 67 patients examined, 22 cases of constant strabismus were found (appendix No. 2). This proportion is at least 20 times the incidence of squint in the general population. If to these are added the inconstant squints and the number who converge spontaneously or irregularly, then some form of noticeable convergent muscular anomaly was found in more than one half of the mongoloids. The deviation was always convergent and horizontal. Vertical deviation or ocular torticollis were not seen. The presence of divergent strabismus is not recorded in the literature.

The commonest causes of convergent strabismus in ordinary ophthalmic practice are muscle pareses, hypermetropia and anisometropia. Developmental myopia sometimes causes divergent strabismus, and rarely congenital myopia produces convergent squint. Less common causes of dissociation are macular disease, optic atrophy, cataract and corneal opacity.

In mongolism, judging by the changes which have been reported in the brain stem, the commonest factor responsible for the production of strabismus should be muscular paresis. Limitation of abduction is commonly seen, and appears to support this conclusion. That muscle pareses are common is refuted when the vertical muscles are considered. Not one case was found with ocular torticollis or vertical deviation of any significant degree. Among ordinary cases of strabismus vertical anomalies are relatively common.

If a sufficiently large number of mongoloids were examined, some cases with height difference would be found. The risks of muscle paresis in mongolism must be at least equal to those among the general population.

The most surprising feature was the number of cases with bilateral convergent squint associated with abduction weakness of each eye. There were 9 of these cases, and the appearances were at first very suggestive of bilateral paresis of the lateral recti. On further examination 8 were found to have high myopia. (The other patient had dense developmental cataracts, and may have been myopic before their formation.) Chavasse attributed this form of strabismus to congenital myopia. The far point of distinct focusing for uncorrected myopes is close to the eyes, so that the range of clear vision is very small. The benefits of binocular vision are readily appreciated when objects are viewed within this range. As distant objects are too blurred to excite interest, the eyes tend to remain converged, and the person so affected devotes himself to things close at hand. When any muscle remains restricted in activity, secondary changes occur within it and the surrounding fascia. After some months or years these structural alterations lead to permanent reduction of the muscle's excursions. Contracture is typical of long-standing squint, and the differences between paretic and other types do not then exist (Chavasse). The frequency of congenital myopia increasing with development has already been shown to occur in approximately one-third of the patients with mongolism. As most of these do not receive spectacles, uncorrected high myopia has been the most common cause of constant strabismus. The other important cause of squint was found to be some form of cataract. If sufficiently clear images are not received by the maculae, binocular vision is not possible.

The necessary reflexes may be precluded by congenital cataracts, or binocular vision may be broken by opacities developing later in life.

Normal infants usually have an esophoria which gradually weakens and changes to an exophoria during adult life, the change being accentuated by the onset of presbyopia. If dissociation occurs, the type of squint is usually determined by the underlying muscle-balance of the time. In mongolism the excessive power of the medial recti continues, so that, if dissociation occurs, a convergent squint follows irrespective of age. If only one eye is affected, so that it receives distorted and embarrassing images, it will be deviated to permit the suppression of these unwelcome stimuli.

Five patients were seen in whom squint was due to lens opacities. Three of these had congenital cataracts (two arcuate, one lamellar), and two had cataracts developing in adult life.

Isolated paresis of a medial rectus is very rare, so that a divergent strabismus would be extremely uncommon. The medial recti are so strong in mongolism that the usual causes of divergent strabismus fail to operate.

Unlike many of the features of mongolism, the strabismus can be readily explained. The inconstant and variable aberrations of convergence are due to insufficient development of the harmonic accommodation-convergence reflex and to the attempts to obtain clear images by the demands from the frontal cortex.

The most important causes of constant strabismus are uncorrected high myopia and lens opacities. They produce the high proportion of constant squinters in this disease. With the other more expected causes, strabismus is so frequent as to be considered one of the stigmata of mongolism.

EXTERNAL INFLAMMATIONS

Nearly all the older writers emphasise the frequency and chronicity of extra-ocular inflammations, particularly blepharitis and conjunctivitis. Young mongoloids show thin lid margins, healthy surrounding skin, clear conjunctival sacs with white globes and clear corneae. Ocular infections are then not common. Later in life the skin tends to become thicker and rougher, and in the patients so affected conjunctival and lid margin infections increase in frequency.

When the eyes are rubbed frequently, particularly with dirty hands, maceration of the skin, blepharitis and ectropion may be produced. Mongoloids are very affectionate, and in institutions they tend to associate with each other, separating from other

patients who dislike their embraces and kisses. Infection can easily pass from one to another.

In days when efficient antiseptics were not available and institutions were less clean, severe chronic infections of the lids and conjunctivae were common. Trachoma was frequently seen with the usual complications of epiphora, chronic conjunctival discharge, entropion, trichiasis, ptosis, conjunctival shrinkage and corneal scarring. Owing to improved hygiene, sulphonamides and penicillin, infections can now be readily controlled and severe sequelae prevented.

In the present investigations trachoma was noted seven times among males and twice among the females. The youngest patient affected with it was aged 27 years. All eyes were quiescent, but some had extensive corneal pannus, conjunctival shrinkage or trichiasis. Most had chronic epiphora, and this appeared to cause a few to have blepharitis and swollen lid margins. Among the remaining 59 patients only one had active conjunctivitis, and another had blepharitis, although a few had some loose skin flakes between the lashes.

INTRA-OCULAR INFLAMMATIONS

Mongoloids are very susceptible to infections of all mucous surfaces, particularly of the respiratory and gastro-intestinal tracts. Pneumonia, pulmonary tuberculosis and dysentery with their complications, have all contributed heavily to a short expectation of life. With modern methods of prevention and treatment these illnesses are less powerful but still common. What tremendous possibilities for "septic foci" must exist! Yet intra-ocular inflammation is very uncommon, and in the present series evidence of it was only seen once or twice. Case No. 34, aged 27 years, showed bilateral attenuated posterior synechiae, which did not prevent the pupils from dilating fully. They probably resulted from a single very mild attack of iritis many years previously.

Case No. 61, aged 44 years, showed several irregular patches of choroido-retinal atrophy with heavily pigmented borders, perhaps due to an old mild choroido-retinitis. She was highly myopic with large complete crescents and choroido-retinal thinnings, so that the patches may have been primarily degenerative and not inflammatory. The Wassermann reaction of the blood and parallel tests were performed as a routine on admission. No positive reports occurred in the whole series.

In contrast with extra-ocular infections, intra-ocular inflammations were seen no more commonly in mongolism than might occur in the general population.

Discussion

In reviewing the peculiarities of the eyes in mongolism, fundamental defects should be differentiated from those produced secondarily. Where an understanding of normal structure and function is available, this distinction may not be difficult, but where this intelligence is lacking, separation may be impossible.

An abnormal vascular system has been shown to be the cause of arcuate lens opacities. These in turn may lead to disturbances of visual function causing ocular nystagmus or convergent strabismus. High myopia has been shown to be a common cause of bilateral convergent strabismus simulating bilateral sixth (abducens) nerve paralysis. These conclusions are possible from a knowledge of the embryology of the lens, and normal and perverted physiology of binocular vision.

It is easy to imagine other organs in which abnormal vascular supply during early development could lead to secondary structural changes, and then to superimposed functional alterations affecting distant parts of the body. The peculiarities of the palpebral apertures may be due to early developmental defects in the skin, but more extensive investigations are required in this field.

The processes involved in normal and abnormal growth are still too obscure to provide explanations for many of the structural alterations in mongolism, and small variations in the early stages of development may lead to wide differences later in life. In that way the clinical syndrome may be built up from a number of patients, but each may show considerable individual differences.

It is interesting to look for the earliest evidence of disturbance associated with mongolism. In the present series one male showed an incomplete coloboma of one eye. The foetal fissure begins to close at its central end in man at about 11 mm. stage (4 to 5 weeks) and all trace has disappeared by the 15 mm. stage (5 to 6 weeks) (Mann, 1937). The condition in this patient represents a disturbance at about 5 weeks, and it is interesting that he showed the lowest grade of amentia of all, in contrast with the high social position and intelligence of his parents. One case, however, is not enough to eliminate other causes than mongolism. Such cases are valuable because our knowledge of choroidal colobomata is much more accurate than that of disc-shaped cataract, where another case suggested a disturbance between 5 and 7 weeks.

The eyes were surprisingly little affected during the vulnerable organogenetic period up to the third month of foetal life. Cases showing anophthalmos, microphthalmos, orbital cysts or choroidal colobomata were unexpectedly rare. The earliest consistent abnormalities seen in the eyes were the arcuate lens opacities, which

correspond with a foetal length of 35 mm. (8·5 weeks). Their dependence upon abnormal vessels shows that mongolism is established by this period at least. The disturbance which produces the abnormalities in the vascular system could probably determine anomalies in other developing structures. The cause of this disturbance is probably the cause of mongolism itself. Of this we are still ignorant, although many theories have been propounded.

The presence of high myopia in approximately one third of the mongoloids appears to be a most significant finding. Unfortunately our knowledge of myopia is still meagre. If severe myopia could be shown to have a high incidence among the relatives of mongoloids, this would produce good support for a germinal influence in mongolism. If such findings were lacking, the influence of the pre-natal environment would be shown to be important for some cases of myopia. The records would be valuable from either aspect. The observations are simple, as the myopic fundus picture is so easily recognised, and the focus on a direct ophthalmoscope would be adequate if retinoscopy were not available.

Tredgold describes the tissues in mongolism as having a peculiar lack of durability and vitality. Mongoloids are much slower to grow up, never reach proper maturity, and begin to decline earlier. The infants appear to be only about half their chronological age, whilst the older adults look much more than their years. The lack of tissue durability and vitality is seen very well in the vascular iris stroma. To the hypoplasia found in young mongoloids, atrophy is added later and the changes become very marked as age advances. But senile cataracts do not occur unduly early in the lens—a tissue very susceptible to sclerosis with age. In all patients up to 60 years of age, no senile cataracts were seen. Similarly, except in myopia, the retinal vessels and maculae presented no degenerative appearances.

The problem of the cause of mongolism remains unsolved. Developmental anomalies of the eyes, viscera, dermal patterns and cardio-vascular system show that the disturbance begins very early during foetal life. The embryo may be defective from maternal causes alone or from a genetic predisposition that only finds expression in a particular environment. Penrose (1931-1932) has shown statistically the importance of maternal age, and many other workers have further incriminated the foetal environment. The geneticists, while emphasising the major contribution from the environment, point to the studies on twins and the frequency of features usually influenced genetically (*e.g.*, dermal patterns). In mongolism the importance of the environment is so definite, and dysplastic changes so widespread and little understood, that to attempt too much explanation on a genetic basis is

undesirable. It is a disease full of riddles, complicated by incomplete and inaccurate observations. Many aspects are inexplicable until more is known about normal physiology, embryology, and the occurrence of some of its features among the general population.

Summary

The eyes of 67 mongoloids varying in age between one and sixty years, were examined. The series contains 40 adults over 25 years of age.

Mongolism is a syndrome that is recognised by a number of stigmata, each of which is not separately specific for the disease. Those found associated with the eyes were short sloping palpebral apertures, evenly curved upper lid margins, convergent strabismus, nystagmus, characteristic lens opacities, speckling and peripheral atrophy of the iris stroma, and high myopia.

Four adult mongoloid skulls presented considerable dysplastic changes, particularly in the regions where growth is normally pronounced. The slope of the palpebral apertures is shown to be independent of the slope of the orbital axes.

Epicanthus is of the same type found in normal babies. It usually disappears with growth of the face.

The iris often shows thinning of the stroma peripherally, with a speckled appearance due to collections of pigment in a circle concentric with the pupil. Generalised vascular hypoplasia is suggested as the main cause. The changes are not seen in heavily pigmented brown irides.

Lens opacities are very common. Three types are described, the combination of which is characteristic for mongolism. Arcuate lens opacities develop during foetal life owing to the presence of abnormal vessels. Sutural opacities occur mostly within the anterior Y sutures of the foetal nucleus. Flake opacities are found within the juvenile and adult nuclei. The opacities form slowly, progress little and rarely require surgery.

The refractive errors of 35 mongoloids were measured. Two-thirds of them had variations from emmetropia corresponding to the general population. One third had high myopia with the usual fundus changes.

Nine patients were found to have obvious nystagmus. Of these ocular nystagmus due to lens opacities or myopia was present in 7 cases. Aplasia or degeneration of the central nervous system was probably responsible for the remaining two.

Twenty-two mongoloids (one third) had constant strabismus. It was always convergent and horizontal. Eight had bilateral squint due to high myopia. Lens opacities were the cause of 5 cases.

Convergence and accommodation are frequently not co-ordinated, so that excessive convergence is common. Muscular palsies are not important causes of strabismus.

The visual acuity of mongoloids is frequently poor because of myopia, nystagmus, strabismus, lens opacities, and failure to reinforce conditioned reflexes during development.

Where possible, explanations are given for the peculiarities found. Other conditions await further knowledge of normal physiology before the abnormalities in mongolism can be fully described.

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The co-operation, enthusiasm and kindness of the above and their staffs made the work a great pleasure. The friends who have helped me in the preparation of this work are too numerous to mention individually. I must ask them to accept this collective expression of my gratitude.

APPENDIX NO. 1

CONTAINING THE CASE REPORTS OF 9 MONGOLOIDS WITH NYSTAGMUS

OCULAR NYSTAGMUS

(*a*) LENS OPACITIES.

Case 16, *aged* 11 *years.*—R. disc-shaped cataract (no vision). Left arcuate opacity causing mixed astigmatism. Macula appears normal. Eyes parallel. Some nystagmus on fixation, coarse nystagmus to left, fine to right.

Case 51, *aged* 39 *years.*—Pendulum nystagmus on fixation, typical bilateral posterior polar cataracts from hyaloid arteries preventing central vision.

Case 53, *aged* 40 *years.*—Bilateral arcuate lens opacities and constant ocular nystagmus. Right convergent strabismus 45°. Will not fixate with right eye when left is uncovered. Low hypermetrope when retina focused with direct ophthalmoscope. When the fixated object is brought to 3 inches from the nose the excessively converged right eye swings out a little, both visual axes appear directed on the object, and the ocular nystagmus diminishes.

Case 56, *aged* 42 *years.*—Dense congenital lamellar cataracts right and left. Unsuccessful operation on right during childhood. Continual searching movements of head and eyes. If he fixates a bright light, the eyes remain steady as the nystagmus diminishes.

Case 60, *aged* 44 *years.*—Very dense bilateral developmental cataracts of central radiating type (cortical and adult nucleus), coarse rolling nystagmus increased on looking to right or left. Right convergent strabismus of variable angle. Can just see enough to find his way about in familiar places.

(*b*) MYOPIA.

Case 9, *aged* 5 *years.*—Very frequent rolling twitches more noticeable on looking to right or left. Eyes parallel. Media clear. Myope with fundus thinning but no obvious atrophy.

Case 25, *aged* 17 *years.*—Uncorrected high myope with anisometropia and choroido-retinal thinning. Left coronary and sutural lens opacities (see further notes under strabismus). Does not maintain fixation anywhere more than a few moments. Many variable jerking movements on attempting fixation (ocular nystagmus). Nystagmus very coarse, and increased on looking to left (against left internal strabismus) reduced and finer to right.

NYSTAGMUS DUE TO DEFECTIVE NERVOUS SYSTEM

Case 29, *aged* 25 *years.*—Extremely low-grade ament, resistive and impulsive, even fails to recognise his parents. Comes from a high-grade family who did all that was possible, but he has remained in the lowest category. Media clear. Right partial choroidal coloboma and pale disc, but left fundus showed no abnormality, and left macula gave good reflex. No gross refractive error. Will not hold fixation of a light. Constant searching type of nystagmus in all directions. Right convergent strabismus of variable angle.

Case 47, *aged* 37 *years.*—Fundi seen well, so flake lens opacities insufficient to reduce vision, eyes parallel. Low-grade ament. Persistent, variable, coarse nystagmus greatly increased with all movements. On close fixation the eyes become steady.

APPENDIX NO. 2

CONTAINING THE CASE REPORTS OF 22 MONGOLOIDS WITH CONVERGENT STRABISMUS

ACCOMMODATIVE, INCONSTANT, VARIABLE

Case 11, *aged* 9 *years.*—Left eye converges irregularly, slight overaction of inferior obliques on each side on adduction.

Case 58, *aged* 43 *years.*—Parallel for distance, often converges evenly, but on repeated convergence sometimes develops internal strabismus and becomes monocular, can alternate. Low compound hypermetropic astigmatism.

ACCOMMODATIVE—CONSTANT.

Case 23, *aged* 13 *years.*—Alternating convergent squint. Hypermetropia +7·0 D. Can hold fixation with either eye but prefers fixation with left. Abduction weakness more to right than to left; probably due to secondary contracture.

Case 50, *aged* 39 *years.*—Alternating convergent squint about 20°. At times converges spontaneously. After instillation of homatropine and cocaine, eyes became parallel. Low compound hypermetropic astigmatism. Slight overaction of right inferior oblique on adduction.

DUE TO UNCORRECTED HIGH MYOPIA.

Case 25, *aged* 17 *years.*—Uncorrected high myopia with anisometropia. Right myopia approximately −10 D. Both retinae show choroido-retinal thinning. Left coronary and central lens opacities, right lens almost clear. Ocular nystagmus, but only attempts fixation with the right eye. Left convergent strabismus with very variable angle due to influence of frontal cortex in attempting to obtain clear vision by voluntary control over the accommodation-convergence synkinesis.

Case 34, *aged* 27 *years.*—Alternating bilateral convergent squint with limited abduction to right and left. Binocular convergence when object held closely. By retinoscopy myopia −20 D right and left, and wearing −13 D spheres right and left. Fine stretched posterior synechiae. Small arcuate lens opacities at 9 o'clock in each eye.

Case 36, *aged* 27 *years.*—Anisometropia (R.-12D. L-5D.) and prefers fixation for distance with left eye as it has lower myopia. Bilateral convergent squint with marked abduction weakness right and left. Does not appear to become binocular at any distance. When object is close can hold fixation with either eye, but the

non-fixing eye always remains excessively adducted. Bilateral arcuate lens opacities temporally.

Case 40, *aged* 32 *years.*—L.C.C.S. about 20°. High myope, has worn glasses many years although considerably undercorrected. Does not hold fixation long with either eye; will hold fixation a short time with the right eye but quickly gives it up. For quite close, eyes assume equal convergence and appears to fix binocularly.

Case 44, *aged* 35 *years.*—Bilateral convergent squint. Now dense central cataracts right and left. When lenses were clear very high myopia was noted with myopic degeneration of the fundi.

Case 52, *aged* 40 *years.*—Bilateral convergent squint. High myopia but no retinal degeneration. Can abduct fairly well but each eye remains converged about 30° most of the time. Can alternate until the object is very close when she appears to become binocular.

Case 61, *aged* 44 *years.*—Bilateral convergent squint. Can abduct either very little beyond the midline. High myope with some choroido-retinal degeneration, appears to become binocular when object is held very close.

Case 67, *aged* 60 *years.*—Bilateral convergent squint with abduction weakness right more than left. High myope with typical gyrate atrophy. The right eye is more convergent than the left, the atrophic patches are more extensive, and its vision is probably very poor.

DUE TO LENS OPACITIES.

Case 17, *aged* 11 *years.*—R.C.C.S. with right abduction weakness. Right arcuate lens opacity causing considerable astigmatism and leading to amblyopia ex anopsia. Right fundus focuses at zero with direct ophthalmoscope.

Case 27, *aged* 22 *years.*—L.C.C.S. 30° with left abduction weakness. Only fixes light momentarily, and eyes move conjunctively in rapid change of positions. Developmental lens opacities obscure fundi to ophthalmoscopic examination.

Case 53, *aged* 40 *years.*—R.C.C.S. 45° arcuate lens opacities right and left giving very poor vision, although fundi showed no abnormality. Constant searching nystagmus. On convergence fixes with left eye and both adduct until the object is about 3 inches from the eyes. The right eye then swings out until both optic axes are directed on to the object, nystagmus diminishes, and binocular vision seems to occur.

Case 56, *aged* 42 *years.*—Variable convergent squint, visual acuity very poor owing to dense bilateral lamellar cataracts. These were needled during childhood, but the result is poor. The head and eyes undergo continual searching movements.

Case 60, *aged* 44 *years.*—Right convergent squint about 30° but variable. Has dense central developmental lens opacities. Fundi not seen.

DUE TO DEVELOPMENTAL ANOMALY OF RETINA.

Case 29, *aged* 25 *years.*—Right convergent squint of variable angle. Very low-grade ament. Partial choroidal coloboma spreading from right disc downwards and outwards, and appearing to disturb right macula. Constant searching type of nystagmus, although left eye normal in appearance.

DUE TO CORNEAL OPACITIES FROM TRACHOMA.

Case 64, *aged* 46 *years.*—R.C.C.S. 50°. Considerable trachomatous pannus and ptosis. Right pupil smaller than left. Too stupid to co-operate for further examination.

Case 55, *aged* 41 *years.*—L.C.C.S. about 45°. Extensive trachoma of left cornea preventing fundus examination. Right fundus can be seen and focused at -8 D. Fixes steadily with right but cannot fixate with left.

DOUBTFUL CASES.

Case 2, *aged* 1 2/12 *years.*—Convergent squint, probable alternator, conjugate movements appear good. Unable to investigate further.

Case 43, aged 45 years.—L.C.C.S. 45° amblyopic left eye. Compound hypermetropic astigmatism. Retinoscope shows left astigmatism more irregular than right so probably due to anisometropia.

Case 64, aged 46 years.—Bilateral convergent squint with abduction weakness right and left. Now has dense trachomatous pannus and moderately thick lens opacities. Fundi not seen, impossible to estimate refraction. May have been myopic before opacities occurred, but no records available.

Case 65, aged 47 years.—L.C.C.S. about 15° with slight weakness of left abduction. Performed cover test very well. Low compound hypermetropic astigmatism. Some lens opacities, but fundi were seen clearly. Possibly paretic left external rectus.

Case 72, aged 27 years.—Not seen during life but case history records bilateral convergent squint. Brain shown in Fig. 20. Sections through sixth nerve nuclei at different levels showed no abnormality (Prof. R. Willis). No records of refraction, probably high myope.

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SOME CONSIDERATIONS ON THE SALT CONTENT OF FRESH AND OLD OX CORNEAE

BY

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THE transparency of the cornea is closely connected with its water-content (Fischer, 1933; Kinsey and Cogan, 1942); one of the factors determining the water-content of the tissue must be the osmotic forces operating between it and its surrounding fluids, in this case the tears and aqueous humour; and these are of course indicated by the relative concentrations of salts in the tissue and fluids. It is therefore of considerable interest to determine with precision the normal concentrations of osmotically important ions in the fresh tissue and to compare them with those in older and more heavily hydrated corneae.

METHODS

The eyes from freshly slaughtered oxen were brought to the laboratory in an ice-cold container. Water-contents were determined by measuring the loss in weight after about 16 hours at 105°. Chloride was estimated by Van Slyke and Sendroy's (1923) method, modified by filtering off the AgCl precipitate through an asbestos filter before titrating the excess of $AgNO_3$ with KCNS. For sodium and potassium the wet-ashing technique with HNO_3 plus a few drops of H_2SO_4, described by Davson (1939), was employed; the Barber-Kolthoff (1928) and Kramer (1920) methods were applied to the strongly acid ashed residues. Blank runs showed that under these conditions phosphate is not precipitated by the Uranyl-Zinc acetate reagent. Since analyses were generally carried out as single determinations of whole corneae there were no duplicate determinations to give an estimate of likely errors in the chemical work; however, the methods applied have been used for many years in this laboratory with a precision well within a one per cent. error.

RESULTS

The Normal Relationship

The important ions determinable with accuracy are sodium, potassium and chloride; the quantities of these ions in one kg. of corneal tissue are presented in Table I; for comparison the values for the aqueous humour are shown in the same table. Before any deductions may be drawn from the comparative ionic contents of cornea and aqueous humour, however, we must express the figures in comparable units. At first thought it might be considered sufficient to express the figures simply as so many millimoles per kg. of water, but a further correction is necessary for the corneal figures for the following reason. We are concerned with the osmotic relationships between the aqueous

humour on the one hand and the fluid from which it is separated by the corneal endothelium. That is, we are concerned with the extra-cellular matrix of the cornea; and since a part of the tissue is made up of cellular elements, we must deduct their contribution to the apparent concentration in the whole cornea. In Table II only the first correction has been made, the results being converted into millimoles per kg. of water. The non-cellular water is calculated on the following basis. The concentration of potassium in the cornea is 23·4 millimoles per kg. of cornea, or 29·4 millimoles per kg. of water; it is a fair assumption that the

TABLE I

Salt content of cornea and aqueous humour in mmoles/kg. cornea

(The figures presented here for corneal sodium and chloride are derived from 35 eyes; for potassium 46 eyes, and for water-content 87 eyes. Standard errors are indicated.)

	Sodium	Potassium	Chloride	Water per cent.
Cornea	115 ± 0·7	23·4 ± 0·8	79·6 ± 1·2	77·9 ± 0·3
Aqueous	148 ± 0·8	7·0 ± 0·4	123 ± 2·2	99

TABLE II

Salt content of cornea and aqueous humour in mmoles/kg. H_2O

	Sodium	Potassium	Chloride	Water per cent.
Cornea	147·2	29·4	99·6	77·9
Aqueous	149·5	7·1	124	99

high concentration in comparison with that in the aqueous humour or plasma is due to its accumulation within the cellular units of the cornea. If we assume that the concentration in the non-cellular water is the same as in plasma, *i.e.*, 6 to 7 millimoles/kg. H_2O; and that the concentration in the cellular water is 165 millimoles/kg. H_2O, we can calculate how much cellular water is present to give a bulk concentration in the whole cornea of 23·4 millimoles per kg. The calculation indicates that some 15 per cent. of the water in the cornea is intra-cellular. In Table III the figures have been expressed in millimoles of ion/kg. of

TABLE III

Salt content of corneal *extra-cellular fluid* and of aqueous humour in mmoles/kg. H_2O

	Sodium	Potassium	Chloride	Bicarbonate	Total
Cornea ...	173	6.5	120	35	334·5
Aqueous ...	149·5	7·1	124	36	316 6

extra-cellular water; from these we see that the concentration of sodium is some 15 per cent. higher in the corneal extra-cellular water than in the aqueous humour, whilst the chloride concentration is rather less in the cornea. The demands of electrical neutrality require that the number of positive ions in the aqueous humour be equal to the number of negative ions; this necessitates that the bicarbonate concentration should be 36 millimoles kg. H_2O if allowance is made for the calcium and magnesium present. In the cornea, even after allowing a proportional amount of bicarbonate, there is an anion deficit of about 30 millimoles; and it is reasonable to suppose that this is accounted for by the collagen and hyaluronic acid anions. Qualitatively we may say that the ionic distribution may be represented by the scheme :—

Cornea	Aqueous
NaX	
NaCl	NaCl
$NaHCO_3$	$NaHCO_3$

where cations other than sodium are ignored and X refers to colloidal anions. The total estimated concentration of ions is 334·5 millimoles/kg. H_2O; and since that for the aqueous is 316·6 millimoles/kg. H_2O, the results suggest that the osmotic pressure of the extra-cellular fluid is greater than that of the aqueous humour. As a possibility this, of course, cannot be put out of court, especially in view of the continued evaporation from the corneal surface. The more serious objection is that we should expect, on the basis of the scheme illustrated above, the excess of sodium in the cornea over that in the aqueous humour to be balanced by an equivalent deficiency of chloride and bicarbonate, as occurs in the erythrocyte, for example. It is unlikely that this

excess of chloride is due to a non-specificity in the method of estimation; moreover, the figure presented here is in fair agreement with that given by Fischer (1933). It is possible that the thermodynamic activity co-efficients for the chloride-ion in the protein-rich cornea is much less than unity, in which case the excess of chloride would only be apparent.

Change of Salt-Content During Storage

After 24 hours in the ice-chest the appearance of the cornea in the excised eye has radically changed; it is no longer clear but smoky and its thickness is found to have increased quite obviously on cutting it up. Numerous experiments have been carried out by the author on the changes of water, sodium, potassium and chloride in the cornea during this ageing process; details of a single experiment agreeing substantially with all the rest will now be presented.

Eighteen fresh eyes were obtained, nine were placed in the ice-chest for 24 hours, whilst the corneae of the remainder were immediately cut up into four pieces, one for sodium determination, one for potassium, one for chloride, and one for water-content. Since the quantities provided by a single cornea were inadequate for accurate analysis, three pieces from three separate corneae were pooled. The results therefore appeared as three determinations of each ion and of water; the mean of these three thus represented the mean of nine separate corneae. A similar procedure was adopted for the corneae from the eyes allowed to stand for 24 hours overnight.

In Table IV the results have been expressed in millimoles of ion/kg. of cornea. It will be noted that the mean water-content has risen from 77·3 per cent. to 82 per cent.; this is equivalent to an uptake of water of 260 g./kg. of cornea. Sodium shows a slight decrease in concentration, potassium a larger, whilst chloride shows a slight rise. If it is appreciated that the total water-content of the cornea has increased by 260 g./kg. of cornea, the fact that the ionic concentrations have been largely unaffected indicates that the swelling of the cornea has been associated with a migration of salt solution rather than of water alone.

We need not go into the details of the computation here, but, if allowance is made for the intra-cellular water, it appears that the total concentration of ions in the extra-cellular water falls slightly from 337 to 319 millimoles/kg. of water during the ageing process. Since this generally corresponds with a fall in the concentration of salts in the aqueous humour, we may conclude that the increased hydration represents predominantly a migration of aqueous humour into the cornea, and not a mere osmotic drainage of water from this fluid. It should be noted in parenthesis that the potassium content of aqueous humour may increase by 50 to 100 per cent. during a 24 hours storage of the intact eye in the ice-chest. This is presumably due mainly to loss from the

TABLE IV

Salt contents of fresh and stored eyes in mmoles/kg. cornea

Fresh Eyes

	Cornea				Aqueous
	Group I	Group II	Group III	Mean	
Na	117	117	116	116·7	147·5
K	25·3	22·5	29·5	26	6·9
Cl	81·5	80·5	80	81	125·5
HCO_3	—	—	—	20	31·4
H_2O (%)	77·7	76·8	77·5	77·3	99
Total Ions (mmoles/kg.)	—	—	—	244	311
Total Ions (mmoles/kg. Extra-cellular H_2O)	—	—	—	**337**	**314**

24-hr. Old Eyes.

	Group I	Group II	Group III	Mean	Aqueous
Na	116	115	115	115.3	141
K	22·4	20·9	22·1	22	10·6
Cl	83·5	83	84	83·5	122·5
HCO_3	—	—	—	21	30·5
H_2O (%)	81·4	82	82·5	82	99
Total Ions (mmoles/kg.)	—	—	—	242	305
Total Ions (mmoles/kg. extra-cellular H_2O)	—	—	—	**319**	**308**

cellular elements of the iris and lens; we must therefore regard with some suspicion any results on the distribution of potassium between aqueous humour and plasma derived from the studies of dead cattle eyes. It may be that some of the striking results described by Salit (1939) are attributable to this cause.

DISCUSSION

The results described here suggest, but of course do not prove, that the substantia propria is in approximate osmotic equilibrium with the aqueous humour; if there is any significant difference in concentration it is rather in favour of the substantia propria than of the aqueous humour. This observation suggests, but once again does not prove, that an interchange of sodium, potassium, and chloride between aqueous humour and substantia propria is possible. This suggestion is, however, apparently ruled out by the studies of Cogan, Hirsch and Kinsey (1944) and of Holt and Cogan (1946), whose careful researches indicate that the membranes separating the substantia from the aqueous humour on the one hand, and tears on the other, are impermeable to salts although permeable to water. Whilst their results do not necessarily prove a complete absence of a transfer of salt,* we may conclude that salt exchanges are much more likely to occur between substantia propria and tissue fluid in the region of the limbus, and thence by diffusion into the axial region of the cornea. As the cornea ages, a considerable migration of salt solution into the substantia propria takes place. Thus the endothelium of the cornea permits the transfer of salts under these conditions; it is likely that this is an abnormal leakiness of the endothelium, although in view of the length of the times concerned, this transfer may be due to a normal small permeability to salts. This brings us to the problem of the normal turgescence of the cornea and its transparency. Fischer drew attention to the fact that the excised cornea placed in saline swells to a great volume; Cogan and Kinsey (1942) have emphasised this point and have drawn attention to the fact that the cornea is in contact with a saline solution at the limbus and might therefore be expected to swell by abstracting water from this region as well as from tears and aqueous humour. They developed a fluid-transfer theory of the normal maintenance of the deturgesced state of the cornea based on a turgescence at the periphery associated with a continuous abstraction of water from the more axial regions, resulting from the supposed difference of osmotic pressure between aqueous

* Complete impermeability to salts is a rare phenomenon in cells and tissues; studies with Radio-Na indicate a very slow transfer into the substantia propria through the corneal epithelium; removal of the epithelium permits a very rapid transfer into the substantia propria but migration into the aqueous humour is impeded by the endothelium. Thus in one hour the concentration of Radio-Na in the aqueous humour of an ox eye, suspended in a Radio-Na solution such that the cornea was just covered, was 0·8 per cent. of that in the outside medium. If the epithelium was stripped the result was approximately 25 per cent. It would seem that the endothelium was about 7 to 8 times more permeable to Na than the epithelium. It is possible, indeed probable, that degenerative changes had already occurred although the eyes were kept ice-cold during transfer from the slaughter-house; there is no reason to believe, however, that the corneae were in any worse state than those on which permeability studies have been made in the past.

humour and tears on the one hand, and the stroma of the cornea on the other; *i.e.*, they assume that tears and aqueous humour are hypertonic to the stroma. This theory, attractive at first sight, runs into difficulties on near investigation. As the present results show, and as may be confirmed by numerous investigations on simpler colloidal systems, corneal stroma increases its water-content by the imbibition of a saline solution and not merely of water; this follows automatically from the Donnan-Equilibrium theory of gel swelling. If, therefore, there is a continuous absorption of water at the periphery of the cornea, there must also be an absorption of salt; the abstraction of water alone from the stroma, by the supposed difference of osmotic pressure, will lead to an accumulation of salt in the stroma tending to abolish the difference of osmotic pressure necessary for the removal of water. This excess of salt would, of course, tend to diffuse back to the limbus, but it seems to the author that on kinetic grounds the osmotic mechanism, regarded as a means of maintaining the cornea in a deturgesced state, would be very inefficient—salt and water entering by flow; water leaving by flow over a large available surface and salt only by diffusion through a restricted surface. The mechanism depends, moreover, on a supposed difference of osmotic pressure between the stroma and tears, effectuated by the corneal epithelium which is impermeable to salts. Tears are said by Krogh (1945) to be isotonic with blood but this of itself is no serious objection since we may assume that their effective concentration on the surface of the cornea is considerably greater, on account of evaporation. It is known, however, that closure of the eyes for long periods, as in sleep, does not cause an oedematous condition of the cornea; moreover, stripping the corneal epithelium, thereby preventing any difference of osmotic pressure from acting, likewise does not cause any optically noticeable increase in hydration of the cornea during the 24 hours required for its regeneration.

Thus as an adequate explanation for the normal deturgesced state of the cornea, the theory of Cogan and Kinsey cannot be readily accepted; whether some modification could meet the objections raised here it is difficult to say.* In the view of the author, any theory that ignores, or attributes a minor rôle to vital activity on the part of the cellular constituents of the cornea—epithelium, endothelium, corneal corpuscles—is unlikely to prove

* Attention has been drawn elsewhere (Davson, 1949), to the fact that there is no need to assume, as earlier authors have done that there is any tendency for the stroma to absorb water from the aqueous humour and tears. Because of the impermeability of the lining membranes to salts, a Donnan swelling is impossible, in the same way that the erythrocyte does not swell up and burst although it contains a 30 per cent. solution or gel of haemoglobin; If the membrane is made permeable to salts the Donnan swelling occurs (*vide e.g.*, Davson and Ponder, 1940). Similarly the swelling described in this paper must be regarded as a result of a permeability of the endothelium to salts occurring as a degenerative change.

fruitful. Superimposed on any physical conditions favouring a dehydration of the colloidal constituents of the substantia propria there must be an over-riding chemical control dependent on the metabolism of the cornea as a whole. The studies of Fischer, and more particularly of Cogan and Kinsey, have clarified many of the physico-chemical aspects of corneal hydration in a valuable manner; further research must follow on an exact analysis of the changes occurring under conditions of disturbed metabolism. Thus it has been shown by Pirie, Schmidt and Waters (1948), that the corneal collagen is at its swelling *minimum* in the physiological range of pH, and that on the acid side of this minimum the swelling curve rises steeply. Work on the cornea has been largely carried out on the excised eye; if this is dying we must expect an increased acidity of the medium and thus a large increase in turgescence. It would be quite wrong to say that the normal cornea must possess a mechanism for preventing this, over and above the normal vegetative metabolism which preserves the physiological pH. It should be noted that the iso-electric point of the corneal stroma, as opposed to that of collagen, is not pH 7·4 but on the acid side; presumably this is due to the hyaluronic acid present.

Summary

The distribution of sodium, potassium and chloride between the corneal extra-cellular water and aqueous humour in fresh and stored ox eyes has been determined. It is shown that the increased hydration of the cornea accompanying storage is associated with the migration of salts so that, in effect, aqueous humour, and not merely water, is taken up.

The results are discussed in relation to current theories of corneal transparency.

I am indebted to Miss P. A. Matchett for carrying out many of the chemical determinations.

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AN ADVOCACY OF EXTERNAL DACRYO-CYSTORHINOSTOMY*

BY

F. N. SHUTTLEWORTH

LEEDS

ALTHOUGH the British ophthalmologist has not adopted Toti's operation or its modifications, in the treatment of chronic dacryocystitis, with the enthusiasm of his Continental colleagues, the British ophthalmic literature of the past fifteen years contains articles extolling the superiority of this operation over the simple excision of sac. Traquair, 1932 and 1941, Lyle, Cross, Simpson and Fraser, 1948, have all published figures with a high percentage of successes, which are in themselves a forcible recommendation for this operation.

This paper is based on the cases of external dacryocystorhinostomy, sixty in all, performed in the Leeds General Infirmary between October, 1941, and December, 1947. The operation was undertaken infrequently at first, but its frequency increased as its good results became obvious and its comparative simplicity was realised. Now it is the operation of choice for chronic dacryocystitis up to the age of sixty years.

The purpose of this article is not to quote further results in complete agreement with those already published, but rather to show that the exact technique is not of very great importance, and that the operation can be undertaken with equally good results by the less experienced ophthalmic surgeon. Traquair emphasises this when he says, speaking of external dacryocystorhinostomy . . . " gives excellent results even in the hands of relatively inexperienced operators."

In the sixty cases quoted, the operation was an external dacryocystorhinostomy, and only two were carried out with the assistance of an E.N.T. surgeon, once to assist an ophthalmic chief, and once to assist an ophthalmic registrar. The numbers are divided more or less equally between the two ophthalmic firms of the Leeds General Infirmary, each of which has its own method of performing the operation.

Method " A." Except for details of local anaesthesia, the technique is substantially that of Traquair. The anaesthesia is produced by the Moffett method of postural anaesthesia for intranasal surgery, using Brompton cocaine solution,

cocaine hydrochlor. grs. 26.
2 per cent. soln. potass. sulph. $\frac{1}{2}$ fl. oz.
soln. acid carbol. 1 : 500 ad. $1\frac{1}{2}$ fl. oz.
liq. adren. 1 : 1000 to be added 1 : 3.

* Received for publication, May 26, 1948.

Intra-nasal anaesthesia takes thirty minutes, is complete by this method, and is supplemented by infiltration of the tissues in the lacrimal sac area and the infra-orbital notch, by 4 per cent. novocaine with 1 min. of 1 : 1000 adrenalin per c.c. added. The anaesthesia so produced is intense, and complaints of discomfort from patients are very infrequent. After the usual incision through the skin, the sac together with the periosteum of the anterior lacrimal crest and fossa is displaced laterally, by a dental packing tool (Claudius Ash No. 178, stainless steel) as modified

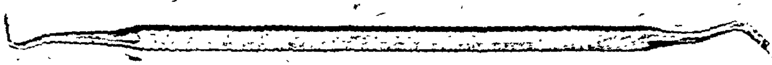

FIG. 1.
MODIFIED DENTAL PACKING TOOL.

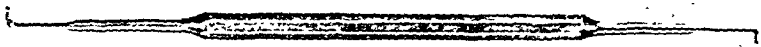

FIG. 2.
MUCOUS MEMBRANE SEPARATOR.

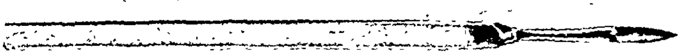

FIG. 3.
SPEAR-POINTED TENOTOME.

by Marshall of Glasgow (Fig. 1). Traquair's mucous membrane separator (Fig. 2) is used to find the weakest point of the floor of the lacrimal fossa, to break through it by gentle pressure, and then to separate the nasal mucous membrane before inserting the small Kofler's punch forceps to cut away the bone of the floor of the fossa and the lower part of the anterior lacrimal crest, down to the level of the inferior orbital margin, thus exposing the top of the lacrimal canal. The mucous membrane separator is invaluable if a friable nasal mucous membrane is to be preserved intact. The bone is removed over a rhomboidal area approximately 1·75 x 1·25 cm., and the nasal mucous membrane so exposed, is cut on three sides to form a flap, the intact side being anterior. The

medial wall of the sac is removed and the flap of nasal mucous membrane turned forwards and sutured to the sac, over the entrance of the canaliculi. The duct is syringed on the fourth day. The patient goes home on the fifth day. The operation takes thirty to thirty-five minutes.

Method "B." General anaesthesia is employed, and the nose is packed pre-operatively with ribbon gauze soaked in 20 per cent. cocaine plus 1 in 1,000 adrenalin. The floor of the lacrimal fossa is prepared as in Method "A." The anterior lacrimal crest is removed by means of a hammer and chisel, the floor of the fossa with Dupuy-Dutemps forceps. The only mucous membrane so exposed is incised to produce a flap with its base hinged posteriorly. The lacrimal sac is incised to produce a similar flap hinged anteriorly. No attempt is made to suture the nasal and lacrimal mucous membranes. A rubber tube is inserted *via* the nose, and its end lies between these two flaps. The tube remains concealed, but is held by a silk stitch which is tied on the surface.

ANALYSIS OF RESULTS

Results	Staff Surgeons		Registrars	Per cent.
	Method "A."	Method "B"	Method A & B	
* No passage	1	2	2	8.5
Passage clear but occasional epiphora	5	2	2	15
Passage clear, symptom-free	18	14	14	76.5
	24	18	18	60

* (1) Patient had a Toti operation performed in February, 1943. Since then she has had alcohol injection of lacrima gland, incision of ductules and excision of lacrimal gland region, and still complains of epiphora, though the lids are not stuck in the mornings.

(2) Patient had a Toti operation performed in June, 1945. The duct was not patent and the lacrimal sac area was re-opened on 1st April, 1946. The remains of the sac were incised; the window in the lacrimal bone was reported as "filled with bone."

(3) Patient had a Toti operation performed in December, 1945. She has considerable trachoma-scarring of both lids and ectropion. No pus is regurgitated upon pressure over the lacrimal sac area.

Twenty-five per cent. of these cases have been seen from one to four years after operation. A further fifty-four per cent. have been seen from three to twelve months after operation.

The anterior flap is sutured to the inner end of the internal palpebral ligament, and so conceals the end of the tube. The skin is sewn up by interrupted sutures. The tube is removed *via* the nose on the seventh day.

From the figures it will be seen that results are equally good whether an exact anastomosis between the nasal mucous membrane and the remains of the sac is achieved or not. It will also be seen that equally good results have been achieved by the less experienced operators, the eighteen cases in the third column having been operated upon by five different ophthalmic registrars between 1942 and now. These figures, too, agree remarkably with those quoted by others. Traquair, for example, quotes 80 per cent. successes when using a flap of nasal mucous membrane, and 71 per cent. successes when using no flap. (In a personal communication to Mr. John Foster, Traquair estimates successes now at 90—95 per cent.) Lyle *et alii* quote 78 per cent. complete cure, 13 per cent. much improved, and 9 per cent. no improvement, using an anterior and a posterior nasal mucous membrane flap.

Tyrrell (1944-45), in a film shown to the Royal Society of Medicine, claimed to perform external dacryocystorhinostomy in ten minutes, using three blows of a hammer and chisel to remove the anterior lacrimal crest and making no attempt at an anastomosis. He recommended frequent post-operative syringing to preserve patency, and estimates 50 per cent. successes.

Spaeth, in his "Principles and Practice of Ophthalmic Surgery," describes numerous methods of performing this operation, the main variations being in the manner of performing the osteotomy and in the preparation of the anastomosis—from two flaps to no flaps. It is sometimes said that numerous methods of carrying out one task mean that no one method is a successful one, yet this is hardly true of the external dacryocystorhinostomy. It would seem that the essential feature is an adequate opening through the bone into the nose, rather than careful anastomosis between the nasal mucous membrane and the remains of the sac.

From the successful cases in this series, certain features stand out:—

(1) Whilst in all cases the anastomosis was patent upon discharge from hospital, three cases, which failed to attend for some time, were found to be blocked when next seen. The interim period varied from three weeks to two months. All were probed and then syringed. When last seen, from two months later in one case to seven months in another, all three were patent; two symptom-free and the third with epiphora in cold weather: Because of this, I feel that regular syringing for a time after operation has value.

(2) On three occasions in the past twelve months, the bony window has opened into ethmoid cells. Whilst this complication had made the operation technically more difficult, the end results have been satisfactory.

SUMMARY

(1) The results of sixty cases of external dacryocystorhinostomy operation performed in the Leeds General Infirmary are reviewed.

(2) Consideration of the figures show little difference in the results :—

(a) Of the two different methods employed, or

(b) The experience of the operators.

I wish to thank both Mr. J. Foster and Mr. G. W. Black for permission to carry out this review, and for their helpful criticism.

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VISITS TO CONTINENTAL OPHTHALMIC CLINICS, 1948

UNDER the auspices of the Faculty of Ophthalmologists three parties, each of some twenty ophthalmologists, visited clinics on the Continent in the summer of 1948. A debt is owing to the Professors and their assistants at the several clinics visited, and they will be interested to hear of the eulogy with which their efforts are related, and the gratitude with which they are remembered.

The HOLLAND visit was organised by John Foster (Leeds), who reports that at Leiden the party was received by Professor van der Hoeve, the doyen of Dutch ophthalmology. A series of papers was read by the Professor and his assistants. Dr. Copper has modified and developed the Piezometric device of Guttman

(*Zeitschr. f. Augenheilk.*, 1914, 31, 4), and produced new figures of orbital impressibility for a variety of conditions. Dr. Binckhorst gave an account of twelve cases of toxoplasmosis hominis, in which organic disturbance of the central nervous system was associated with choroidal lesions. Mrs. Dr. Kok advocated square keratoplasty for adherent leucomata of irregular thickness, and round grafts where operation was expected to be simple, or good appearance essential. Dr. Pieck performed one round and one square keratoplasty, the first by the technique of Franceschetti, the second by that of Castroviejo. Professor van der Hoeve read a paper on lipoidosis, including: (*a*) Niemann-Pick disease and amaurotic idiocy (lecithin), (*b*) Gaucher's splenomegaly (cerebrosin), (*c*) Schilder's disease and xanthomatosis (cholesterin).

UTRECHT. Professor Weve received us at a conversazione at which he showed films of intracapsular extraction and Toti's operation. Dr. Fischer gave demonstrations of Goldmann's method of gonioscopy, the reflectograph which shows minute corneal irregularities, and the cobalt lamp for refraction invented by Russler in 1930. In-breeding in the nearby villages of Walcheren and Spakenburg has produced widespread familial keratoconus, and a special contact-lens clinic is run by Mrs. Dr. Fischer to meet this problem. The lenses are made by fusing old X-ray plates by blowpipe on to plaster casts of corneal moulds.

Black caps, walls and gowns, and grey masks attached to a special operating spectacle, make Professor Weve's theatre an unusual sight. Intracapsular extraction is performed conventionally except for pre-operative tonometry and retraction sutures held by an assistant. In detachment operations the tear is localised on the sclera by the glow point of indirect ophthalmoscopy. The diathermy is directed exclusively against the hole. Over a thousand dacryo-cystorhinostomies were carried out between 1917 and 1937, partly by Toti's and partly by Dupuy-Dutemps' method.

GRÖNINGEN. Professor Rochat (now Emeritus) demonstrated the auto-refractometer with which he has established the occurrence of diurnal variations in astigmatism, up to 1 D. A film of cyclodialysis inversa (Blaskovics), and gonioscopic appearances of successful cases was demonstrated by Professor Dekking. A case of retinitis pigmentosa was treated by ktanotherapy. (Six c.c. of fresh iced placenta were dipped in penicillin and buried under the conjunctiva. A big reaction often follows.) Models of a dark-adaptation test, a binocular ophthalmoscope, and a hand slit-lamp (designed by Professor Dekking and made in the University workshop) were demonstrated.

At AMSTERDAM Professor Hagedoorn demonstrated intracapsular extractions, needling, and squint operations, a device

for measurement of orbital impressibility, cases of fascia lata graft, of resection of the ciliary ganglion for pain, and of tetanic cataract following irradiation of the thyroid. Papers were read by Dr. Adema on "Reefing as treatment of squint," and "Total corneal transplant" by Winckelmann.

Mr. Foster adds, "I would like to offer our thanks once again to our hosts, for (to paraphrase a current advertisement) "Wat der Nederland doet, doet der Nederland goed."

PARIS. The visit was arranged by R. J. Buxton (Yeovil), who sends the following report:—

After a clinical meeting at the Hôpital Quinze-Vingt, Dr. Hartmann showed cases at the Hôpital Lariboisière, and held a demonstration in the use of the tonometer. The diastolic pressure was useful in diagnosing cases of early cerebral tumour and concussion. Dr. Hartmann further discussed corneal graft technique, and showed patients with very satisfactory results. On the next day (Tuesday) we saw Dr. Schiff-Wertheimer and Dr. Dollfuss operate. One retinal detachment was treated by surface coagulation and perforations, and another by the actual cautery; intra-capsular operations were performed. Dr. Monbrun showed cases of tuberculous choroiditis, many of which had been successfully treated with streptomycin. He identified three types of fundus lesion in tuberculosis: (1) disseminated choroiditis, (2) tuberculoma (single large lesion) (3) optic disc lesions. Streptomycin was apparently not toxic to the optic nerve, but the latter might be compressed by organisation of exudate.

Dr. Favory demonstrated two intra-capsular extractions with forceps, and later we were shown round the dermatological museum by Dr. Reynard. We saw a case of leprosy with pathognomonic granules on the iris, and paintings of retinal angioïd streaks associated with pseudo-xanthoma. Placental grafts were being tried for retinitis pigmentosa.

Dr. Hartmann demonstrated cataract extractions. Atropine, cocaine and adrenalin drops were used, no suture was inserted in the lower lid, and no speculum was employed. After dissecting the conjunctiva from 3 to 9 o'clock, the incision was made with a keratome and enlarged with scissors; two iridotomies were made, and three corneoscleral sutures inserted. In a corneal graft operation by Dr. Offret a Franceschetti's trephine (made by Grieshaber) of 5 mm. diameter was used, and then a graft cut without shelving the edges. The graft was kept in place by standard criss-cross sutures. Dr. Offret also gave a lecture at the Hôtel Dieu dealing with reticulo-sarcoma. He also spoke of

familial keratitis; there are two dominant types, (*a*) Groenouw, and (*b*) *grillagée* (lattice), and one recessive-*tâchete* (dotted). The differentiation is important, as the Groenouw type can be treated by lamellar rather than whole-thickness grafts of the cornea.

We returned full of memories of a most enjoyable week, much impressed by the tempo of Paris life. We owe our most sincere thanks to our French colleagues for the organisation of the visit.

SWITZERLAND. Tour organised by W. M. Muirhead and A. B. Nutt (Sheffield).

GENEVA. J. H. Doggart (London) reports as follows:—

Professor Franceschetti and his two Chief Assistants, Dr. Bischler and Dr. Blum, demonstrated cases, performed operations and reviewed the effects of certain new drugs. Dr. Bourquin's laboratory display of familial and hereditary degeneration of the cornea, neatly classified and vividly described, was a privilege to attend. Another particularly fascinating item was Dr. Klein's work on inherited ocular disease.

An eminent gynaecologist, Professor H. de Watteville, reminded us that the influence of the sex-hormones far transcends their effect upon the sexual functions. Various disorders of the pituitary gland, including the Laurence-Moon-Biedl syndrome, were also reviewed in so far as gonadotrophic hormones offer a clue to the diagnoses. Professor de Watteville's teaching, supported by a number of specimens and microscopical slides, opened up an endless vista of the influence that may be exerted upon general metabolism by the sexual hormones.

Many of Professor Franceschetti's clinical investigations have been pursued jointly with Dr. F. Bamatter, who reviewed the literature on toxoplasmosis, and went on to describe the clinical and pathological phenomena observed in the victims of this protozoal infection. He stressed the importance of identifying protozoa in stained tissue sections or discharge obtained from the host, or else indirectly by means of animal inoculation. We were shown old fundus lesions in a number of cases. The typical disturbance consists of a large irregularly shaped, craggy-looking area of old choroido-retinitis. Treatment mainly consists of sulphonamides parenterally administered. Rabbits, guinea-pigs, dogs, cats, sheep and rats have all been shown capable of harbouring and transmitting the parasites.

Professor Franceschetti, who is a dexterous and experienced corneal grafter, reviewed the various types of graft, including the total superficial variety favoured by Sourdille, and the rectangular

section adopted by Castroviejo. Professor Franceschetti himself uses a circular whole-thickness graft of 3 to 8 mm. in diameter, and regards 5·1 mm. as the optimum. This last-mentioned size is placed into a slightly smaller (5 mm.) gap in the recipient cornea. Many technical details were subsequently demonstrated on the operating-table by Professor Franceschetti and Dr. Blum. One aspect of grafting stressed by Professor Franceschetti was the differential prognosis. Some of the most successful results have been obtained in various forms of corneal dystrophy.

The Professor is a great host, an inspiring teacher, and a guest who will always be welcome in Great Britain.

ZÜRICH. Lectures and demonstrations by Doctors Huber and Verrey were devoted to the work on changes in the aqueous humour and blood-aqueous barrier studied by chamber puncture, and observations on the Tindall phenomenon and fluorescein test investigated at Zürich for the past nine or ten years. This has already been described by Professor Amsler in the Bowman lecture to the Ophthalmological Society of the United Kingdom in 1948.

Professor Amsler gave four lectures. The first was on "Keratoconus; diagnosis of formes frustes." By "Keratoconus fruste" is meant the slight, often abortive, type of conical cornea which was not recognised until it was demonstrated by Amsler, and since the cornea is not obviously conical even when superficially examined with Placido's disc, it is apt to be missed unless one is aware of its existence. It accounts for at least some cases of unexplained irregular astigmatism. It is spotted most easily in routine refraction work when the Javal-Schiötz ophthalmometer is used, and in retinoscopy is suggested by the presence of a central "shadow" which rotates around a central point as the mirror is moved to and fro. The diagnosis is confirmed by means of the special Placido's disc designed by Amsler. In addition to the black and white rings, it has white cross markings, is self-luminous, and is combined with a camera which photographs the corneal Placido image. The advantage of the camera is that in very slight keratoconus the small distortion of the Placido image can best be noted by studying photographs thereof. By this means it is observed not only that the rings are narrower in one quadrant (lower temporal) than in the opposite quadrant (upper nasal), but that the horizontal limbs of the cross are at an angle to each other. Amsler measures the degree of keratoconus by reference to this angle between the horizontal white lines. He has thus divided keratoconus into four stages: K. I, when the angle is less than 5 deg.; K. II, when the angle is 5 to

10 deg.; K. III, over 10 deg. (*i.e.*, macroscopic conical cornea, but without central opacity); K. IV, conical cornea with central opacity.

As a result of these observations several facts have come to light: (1) Mild degrees of keratoconus which may or may not progress are more common than has hitherto been thought. (2) Keratoconus is more commonly bilateral than has been realised hitherto. (3) It is more commonly familial than is realised. (4) It has been confirmed that the distortion of the cornea is always in the same direction—the apex of the cone is displaced downwards and outwards.

For treatment of keratoconus Amsler recommends: (1) For K. I, cylindrical correction decided by subjective means. (2) For K. II, the same or a contact lens. (3) For K. III, a contact lens. (4) For K. IV, *keratoplasty is preferred to Sato's operation.*

Professor Amsler's other lectures were upon detachment of the retina, tests for macular function, and the technique of corneal grafting. The enthusiasm and hospitality of the professor and his assistants were greatly appreciated and will not be forgotten.

BERNE. P. McG. Moffatt and C. Dee Shapland (London) report that the party met Professor Goldmann at the University Eye Clinic. His first lecture was on gonioscopy, and was followed by a demonstration of cases showing normal and pathological filtration angles. The Haag-Streit slit-lamp with the Goldmann deviation prism and gonioscopy contact lens were used for these cases, and an opportunity given to each member to become acquainted with their use.

The main value of gonioscopy is to determine pre-operatively which type of glaucoma operation to perform. For the narrow angles which accompany the shallow anterior chamber of congestive glaucoma, and in which the obstruction would appear to be between the root of the iris and the back of the cornea, Goldmann advises iridectomy, preferably by Dieter's method. For the wide angle type, in which the anterior chamber is often deep, and in which the obstruction would appear to be in the trabeculae, cyclodialysis by a slight modification of Blaskovics' method is the operation of choice.

On the next day Professor Goldmann lectured to us on (1) the slit-lamp examination of the fundus oculi with a contact glass, and (2) the localisation of non-magnetic intra-ocular foreign bodies. Retinal biomicroscopy, besides affording a much enlarged and stereoscopic view of the fundus oculi, is of definite value in the differential diagnosis of obscure macular conditions, *e.g.*, holes.

cysts or oedema, and should prove of great value in research, as in detachment of the retina. Professor Goldmann also gave a short talk and demonstration on the aqueous veins which he had discovered shortly after, but independently of, Ascher.

We left with the happiest memories of the quiet courtesy of Professor Goldmann, and with great respect for his ingenuity in diagnostic instrument design.

EYEBALL ROTATING FORCEPS

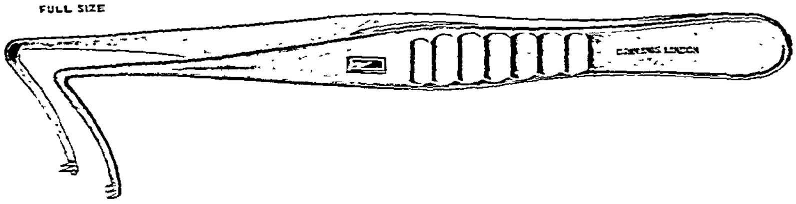
BY

R. LINDSAY-REA

LONDON

EVERY ophthalmic surgeon is aware of the difficulty of rotating the eyeball downwards without obscuring his view. Whether he himself or his assistant holds the conjunctival forceps, the hand holding the instrument comes up and gets in the way.

The idea occurred to me to make a forceps as illustrated. Each blade terminates with a bent arm which is toothed for catching the



conjunctiva. The conjunctiva is seized at 6 o'clock and the spring clip fastened. The forceps then lies on the sterile towel on the patient's cheek. By simply pulling the forceps down, the eyeball can be rotated downwards, the view being uninterrupted. Many uses will be found for this instrument. With it, a muscle suture is unnecessary. It always occupies a place on my operating table.

The illustration was kindly provided by Messrs. Down Bros., who made the forceps. It is also manufactured by Messrs. Weiss and Son.

BOOK NOTICE

Ocular Signs in Slit-Lamp Microscopy. By J. H. DOGGART. Pp. xiv and 112. Ninety-three illustrations (85 in colour). Bibliography. Henry Kimpton, London. 1949. Price 21/-.

This short book is an excellent practical guide to the slit-lamp microscopy of the living eye and will be most useful to the post-graduate student. It could also be read with profit by senior ophthalmologists, many of whom have acquired their slit-lamp technique largely by the light of nature, so that their knowledge of clinical findings is lamentably inchoate and disjunctive. The book does not, indeed cannot within the thin limit of its covers, attempt to give the full and detailed descriptions of various conditions which may be found in such a work as Vogt's monumental atlas, but is indeed no less valuable as affording a short, well-written and stimulating introduction to captivate the tyro's interest in an important method of clinical examination.

The author has relegated his brief historical survey of the development of slit-lamp microscopy to the last chapter, and a technical description of the apparatus to an appendix; discussion of the optical principles he has omitted altogether. He begins his work with a spirited plea for the value of this method of examination and follows with an excellent chapter on the technique of examination in which, it is refreshing to find, every emphasis is laid on the comfort of the patient. Then follow chapters describing the normal eye and pathological changes in the various ocular structures which come successively under review. Throughout, emphasis is laid on what to look for and how to look for it, rather than on detailed descriptions of pathological states, while the general balance of the book appears admirable. The book is well produced, and by no means its least attractive feature is the excellence of its illustrations, the majority of which are in colour. It well deserves, and we are sure it will receive a warm welcome.

OBITUARY

HUNTER McGUIRE

THE death of Dr. Hunter McGuire has deprived American medicine of a great ophthalmologist and a great Southern gentleman. He came of a family of doctors, one of his ancestors, to whom a memorial has been erected in Richmond, Virginia, attended General

Stonewall Jackson at his death. A cripple from birth, he mastered his physical disabilities with remarkable fortitude and success. He was constant in his attendance at meetings of the American Ophthalmological Society and was a favourite with everyone. Unfortunately his visits to Europe were few, as he found sea travel specially difficult. He practised with great success at Winchester, Va., latterly in partnership with his son. To the latter and his sister, Mrs. Macauly Booth, a stage and film actress well-known in England, we offer our sympathy.

NOTES

Award

THE University of Toronto Faculty of Medicine has announced that Dr. J. C. McCulloch has been awarded the Reeve Prize, an award which is made for the best scientific research accomplished in any department of the Medical Faculty by one who has held an appointment on the staff for not more than five years.

Dr. McCulloch was awarded this prize for his study in conjunction with Dr. R. J. P. McCulloch on "A Hereditary and Clinical Study of Choroideremia." Their work has added much to the knowledge of this hitherto obscure hereditary ocular condition. The disease was found in over 80 descendants of a family of 500 subjects studied.

Dr. J. C. McCulloch is Ophthalmologist-in-Chief at Toronto Western Hospital, and was recently appointed Associate Professor, Department of Ophthalmology in the University of Toronto.

* * * *

Ophthalmological Society of Egypt Annual Meeting

THE Annual Meeting of the Ophthalmological Society of Egypt will take place at the Memorial Ophthalmic Laboratory, Giza, Egypt, on Friday and Saturday, March 4 and 5, 1949, at 9 a.m. Medical practitioners, oculists or otherwise, are cordially invited.

* * * *

Royal College of Surgeons of England. Ophthalmology Lectures

THE following lectures will be delivered at the College in Lincoln's Inn Fields, London, W.C.2:—*Tuesday, March 29, 1949,* Professor A. Franceschetti (Prof. of Ophthalmology, University of Geneva), Cataract Associated with Lesions of the Skin, at 5 p.m.; Professor G. B. Bietti (Prof. of Clinical Optics.

Pavia University), Ophthalmic Aspects of Protein Deficiency and Disordered Protein Metabolism, at 6.15 p.m. *Wednesday, March 30, 1949*, Dr. E. Hartmann (Ophthalmologist to the Hôpital Lariboisière, Paris), Psychosomatic Symptoms in Ophthalmology, at 5 p.m.; Professor H. J. M. Weve (Prof. of Ophthalmology, Rijksuniversiteit), Ophthalmic Manifestations of Besnier-Boeck's Disease, at 6.15 p.m.

W. F. DAVIS,
Secretary,
Postgraduate Education Committee.

* * * *

Faculty of Ophthalmologists

THE following is the Honorary Secretary's summary of the business conducted at the last Council Meeting held on December 17.

It was revealed that the memorandum H.M.C. (46) 83, on the development of the hospital eye service, had been prepared by the Ministry under the mistaken impression that it incorporated the views of the Faculty. This document is being revised.

It was reported that the Committee of Management of the Examining Board in England had accepted the recommendations of the Council regarding Diplomas in Ophthalmology, which recommendations will appear in the Annual Report of the Faculty.

As a result of the ballot amongst members of the Council, the following have been elected the representatives of the Faculty on the Ophthalmic Group Committee of the British Medical Association:—Mr. George W. Black, The Hon. G. J. O. Bridgeman, Mr. J. D. M. Cardell, Mr. J. H. Doggart, Mr. O. M. Duthie, Mr. A. B. Nutt,

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Papers submitted for publication should be sent to :—

The Secretary of the Editorial Committee,

British Journal of Ophthalmology,

Institute of Ophthalmology, Judd Street, London, W.C.1

Such papers should be typewritten in double spacing on one side of the paper only, leaving a 1½ inch margin. The Author's name and address should be plainly indicated. References to the literature should be set out in accordance with the Harvard System, *e.g.*, Langley, J. N. (1919).—*J. Physiol.*, **53**, 120. Illustrations should not be fixed to the typescript. They should be numbered in sequence, and the top of each should be clearly marked.

Publication of a paper does not imply that the Editorial Committee agrees with the views expressed therein. The Committee reserves the right to delete redundant words, to modify ambiguous phrases, and to translate foreign idioms into current English expressions. Twenty-five reprinted copies will be sent to the Author (or Authors) of each article free of charge. A form of application will be attached to the Author's galley proofs for any additional copies which the Author may wish to buy.

THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

APRIL, 1949

COMMUNICATIONS

EXPERIMENTAL STUDIES ON THE PATHOGENESIS AND TREATMENT OF OCULAR TUBERCULOSIS*

BY

ALAN C. WOODS

BALTIMORE

Inaugural Address at the Opening of the Institute of Ophthalmology, London

THE investigations which it is my privilege to summarize here have extended over a twelve-year period. Since the more recent studies on the action of antibiotics are as yet in press, it is an additional pleasure to present them here in England, the home of Fleming's and Florey's great and fundamental work, before their actual publication.

A number of my colleagues have participated in this work and are co-authors of the various reports. To these gentlemen I extend

* From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital. These studies were supported by grants from the John and Mary R. Markle Foundation. The technical details of these experiments and reviews of the pertinent literature are given in the various reports on "Experimental Studies in Ocular Tuberculosis" which have appeared or are in print in the Archives of Ophthalmology.

full acknowledgment for the major part they have played in these investigations.

These studies were primarily stimulated by Rich's demonstration in 1929 of the independence of hypersensitivity and immunity, and his explanation then given of the pathogenesis of the tubercular lesion. Prior to Rich's contribution, it was generally supposed that the phenomena of hypersensitivity and immunity were interdependent. Since the time of Koch, it had been clearly recognized that, to comparable doses of the tubercle bacillus, the normal animal reacts in a manner quite different from the animal previously infected with tuberculosis. When the normal animal is infected by the local injection of living bacilli, there is an insignificant reaction at the site of the injection. Thereafter there ensues a slow propagation of the bacilli, involvement of the regional lymph nodes and the formation of hard tubercles. As the infection progresses beyond the local lymph nodes, there follows a widespread systemic infection, first with hard tubercles, which may either become fibrosed, or else necrotic, caseous, and softened. On the other hand, when the previously tuberculous animal receives a comparable injection of bacilli, a sharp inflammatory reaction occurs at the site of the injection. This is characterized clinically by oedema, erythema, induration, and sometimes even by necrosis and sloughing. Histologically this reaction is characterized by a primary outpouring of serum and leucocytes, and later a mobilization of macrophagic cells. The bacilli tend to become fixed at the site of the injection, and, if the infecting dose were small, they may even be destroyed.

The natural deduction from this observation was that the initial inflammatory reaction, which was correctly interpreted as a hypersensitive phenomenon, was intimately related, or indeed responsible for, the local fixation and destruction of the bacilli. In other words, allergy was responsible for immunity. This idea Rich challenged in 1929, pointing out that while this dictum was widely accepted, there was no scintilla of experimental evidence to support it. In a series of brilliant experiments, he and his co-workers demonstrated that there was no relation between hypersentivity and resistance, and that the previously tuberculous animal could be completely desensitized to the extent that not only the soluble bacterial products, but even living bacilli injected in the skin, caused no local inflammatory reaction. At the same time the resistance to dissemination of the bacilli, or immunity to reinfection, was totally undisturbed. As a result of these and other investigations, Rich stated that the factors governing the development and course of a tuberculous lesion could be expressed in an equation, now known as Rich's law. This equation is:—

$$\text{Lesion} \propto \frac{\text{No. and virulence of bacilli} \times \text{Allergy}}{\text{Resistance}}$$

Thus following infection with a moderate or large dose of virulent bacilli, if there is a high tissue allergy and a low immunity, an inflammatory, caseating, necrotizing lesion results. On the other extreme, if the number of infecting bacilli is small, and if there is a low degree of tissue allergy and a high resistance, there will be little inflammation or tissue destruction. Rapid encapsulation and healing occur, and there may even be complete destruction of the bacilli. Varying degrees of infection, allergy and resistance, between these two extremes, explain the various intermediate types of the tubercular lesion.

This concept of the pathogenesis of a tubercular lesion offered obvious therapeutic points of attack. These were, first, an enhancement of resistance which had long been the cornerstone in the treatment of tuberculosis. The second point of attack would be the removal of the fatal tissue allergy, or desensitization. This was something of a new idea, tuberculin previously having been used somewhat disastrously and fruitlessly on the old peri-focal concept, *i.e.*, that since hypersensitivity was assumed to be responsible for immunity, hypersensitive reactions should be encouraged. Thus tuberculin therapy fell somewhat into disrepute. The third point would be a direct attack on the tubercle bacilli, a therapeutic measure which up to that time had been unsuccessful, there being no chemo-therapeutic or antibiotic agent yet demonstrated with any real deterrent action on the tubercle bacillus.

It was the purpose of the investigations which I summarize today to investigate experimentally first, the validity for ocular tuberculosis of Rich's law, and secondly, the therapeutic possibilities suggested thereby.

At the beginning of these studies, there was already considerable reason to believe that Rich's law, or some modification thereof, governed the lesions of tuberculosis in the eye. Primarily, it had been known for some years that experimental ocular tuberculosis ran quite a different course in the normal animal and in the animal previously infected with tuberculosis (the immune-allergic animal). This had been clearly shown as early as 1924 by Henri Lagrange. Secondly, the most striking characteristic of clinical ocular tuberculosis is its amazing pleomorphism. Certainly some extrinsic factors are responsible for the widely varying manifestations of the disease in the eye. The obvious factors are those enumerated by Rich—the dose and virulence of the infecting organism, the degree of tissue allergy present, and the degree of

systemic immunity to infection. It was not known, however, to what extent these factors would be effective on a localized tuberculous lesion in the tightly enclosed scleral and corneal envelope. One troublesome point in the acceptance of this law for ocular tuberculosis was the clear fact that certain experimental animals and humans with ocular tuberculosis showed a high degree of acute inflammation and even caseation in the eye, indicating a high degree of local tissue hypersensitivity, while the cutaneous reactivity of these animals and humans to tuberculin was low or absent.

The immediate objectives of these investigations may therefore be listed as follows:—

I. *Pathogenesis.* Does Rich's law for the pathogenesis of the tuberculous lesion hold true in localized ocular tuberculosis? This was explored by determining: A. The effect of the number and virulence of the infecting organism on the resulting ocular lesion. B. The influence of local tissue sensitivity. C. The influence of systemic immunity. D. The relation of cutaneous and ocular sensitivity.

II. *Therapy.* A. Is enhancement of local resistance or immunity possible? B. What is the effect of desensitization on the local ocular lesion? C. What are the possibilities of sulfone and antibiotic treatment in ocular tuberculosis?

This was an over-ambitious programme. On some points, notably the stimulation of an artificial local immunity, we have not even scratched the surface. On other points, while the work is incomplete and fragmentary, some information has been adduced which confirms the validity of Rich's law on the pathogenesis of the tuberculous lesion in the eye, and strengthens the suggestions for therapy. Some observations have been made on the therapy of experimental ocular tuberculosis which appear to have a bearing on the clinical attack on the disease. These experiments may be summarized as follows:—

THE PATHOGENESIS OF OCULAR TUBERCULOSIS

A. *The influence of the number and virulence of organisms.* The first problem was the determination of the proper strain of tubercle bacilli to be used in the experimental animals and the proper dosage. This was largely a trial-and-error procedure, and it is unnecessary here to go into the various details. Suffice to say that avian and bovine strains proved unsuitable for use in the rabbit on account of the malignant course of the ocular disease

when the organisms were injected into the eye, and the speedy death of the rabbits from generalized tuberculosis when the organisms were injected systemically. A virulent human strain was finally used. Injected into the eye of a normal or immune-allergic rabbit in proper dose, satisfactory lesions developed, and injected systemically, the animals rarely developed widespread tuberculosis, but as a rule developed a self-limiting disease with inconspicuous histological findings, from which they recovered spontaneously, retaining a well developed hypersensitivity to tuberculin, and a definite acquired resistance to re-inoculation—an immune-allergic status. The ocular inoculations were all made in the anterior chamber. Intra-carotid inoculations were unsatisfactory for such a prolonged study as this, because the development of ocular tuberculosis in such animals was a chance and inconstant affair.

When a small dose of the bacilli was injected into the anterior chamber of a normal rabbit, there was a minimal or no local reaction to the injection. About the fourteenth day after injection, these rabbits developed slight peri-corneal injection, slight steaminess of the cornea, and hard tubercles over the iris. About the fourth week this indolent reaction became aggravated, vascularization of the cornea became evident, and acute inflammation, and later, evidences of necrosis and caseation developed. About the sixth week, or thereafter, some of the eyes perforated. In the remainder, beginning about the eighth or tenth week, the acute inflammation began to subside, and the eyes entered the stage of beginning fibrosis. By the twenty-third or twenty-fourth week the disease was usually inactive, leaving blind, scarred and sometimes perforated eyes (Study 2).

When a larger dose of the same virulent organisms was given, this picture was greatly accelerated, the degree of acceleration depending upon the amount of bacilli present in the inoculum. The incubation period before the development of symptoms was shortened to a week or less, the acute inflammatory phase developed rapidly, and perforation of the eyes within four to six weeks was the general rule.

When the eyes of normal rabbits were inoculated with a attenuated strain of human organisms, the results were minimal. The inflammatory symptoms were slow in appearance, and of low degree. Many eyes showed little or no reaction, and those that did show disease usually healed within three months with minimal damage and scarring.

In the immune-allergic rabbit—the animal recovered from a previous systemic infection—the course of the ocular disease after

anterior chamber inoculation was quite different. Primarily in order to produce any tuberculous disease in the eyes of these rabbits, it was found necessary to give a much larger dose of the same virulent bacilli, the minimum dose required to produce low grade tuberculous disease in the eyes of these rabbits being usually fifty times that required for the normal rabbit. When this dose was given in the anterior chamber, there developed within 24 hours a marked inflammatory reaction which subsided within a few days. This was similar to the reaction caused by the anterior chamber injection of tuberculin, and was obviously a reaction to the tuberculo-protein in the inoculum, the eyes, like the other body tissues, having become sensitized by the prior systemic infection. After the subsidence of this tuberculin reaction, the eyes remained asymptomatic for a period of two weeks or longer. Then low-grade ciliary congestion developed, and sometimes discrete tubercles appeared in the cornea and iris. Thereafter the eyes ran a restrained course of chronic inflammation, showing moderate secondary iridic and corneal changes with vascularization. The inflammatory reaction slowly increased, reached a low maximum about the fourth week, continued to the tenth or fourteenth week, and then gradually subsided. The maximum degree of inflammation resulting from the minimal dose capable of producing lesions was decidedly less than that eventually developing in the eyes of the normal rabbits affected with their minimal dose, and perforation practically never occurred (Study IV). In fact, the course of the disease in its various corneal and iris manifestations simulated amazingly ocular tuberculosis in the human adult.

If a larger dose of the virulent bacilli was given to the immune-allergic rabbits, the entire picture was reversed. There was an early violent reaction which never subsided, the eyes rapidly developed a spreading destructive inflammation, with necrosis and caseation, and there was a high percentage of rupture within 6 weeks. The process was even more acute and destructive than the disease in the normal rabbit (Study VI).

When avirulent organisms were given to immune-allergic rabbits, local tuberculous disease did not result, and there was no reaction other than the immediate one to the tuberculo-protein in the inoculum.

From the experiments, it is clearly apparent that the importance of the dose and virulence of the infecting organisms holds true in ocular tuberculosis. In the normal animal with a minimal dose of virulent bacilli, there is a slowly spreading infection, which becomes acute as the organisms propagate and spread through the eye. With a larger dose of the same organisms this reaction is violently accelerated. With avirulent organisms there is little

or no reaction. In the immune-allergic animal, where the propagation and spread of the organisms is restrained by the acquired systemic resistance, after the reaction to tuberculo-protein subsides, the subsequent inflammation is of low degree, and parallels the slow propagation of the bacilli in the eye. However, with a larger dose of bacilli, there is a violent immediate inflammatory reaction, the immunity is overwhelmed, the bacilli propagate rapidly, and necrosis, caseation and rupture occur early.

In the subsequent experiments, in both the normal and immune-allergic rabbit, the minimum dose capable of producing lesions with fair constancy, was uniformly used.

B. *The influence of hypersensitivity on the ocular lesion,* It has already been noted that acute inflammation with necrosis and caseation develops in the normal rabbit as the bacilli propagate and spread through the eye. In the immune-allergic rabbit after the immediate hypersensitive reaction subsides, acute inflammation develops only as the bacilli propagate, is of lower degree than in the normal, and there is minimal necrosis and caseation. What is the relation of this acute inflammation to hypersensitivity of the eye?

The ocular sensitivity can be accurately gauged by the injection of tuberculin* into the anterior chamber, estimating the clinical reaction, and then enucleating these eyes and evaluating the histological reaction. This was done at weekly intervals in sample pairs of rabbits throughout the course of several experiments. Thus a graph could be prepared illustrating the development and the course of ocular sensitivity during any period of observation. Likewise, by clinical estimation on a numerical scale, the degree of ocular inflammation resulting from infection could be estimated in the remaining animals of the group, graphed, and compared with the degree of ocular hypersensitivity as measured by the intra-ocular tuberculin test in the sample rabbits. This was done for both normal rabbits (Study II) and for immune-allergic rabbits (Study IV). The validity of graphs was checked statistically (Study IV).

The results of this graphic study for normal rabbits are shown in Fig. 1, and for immune-allergic rabbits in Fig. 2. The ordinates represent the degree of ocular inflammation and sensitivity and the abscissae the time in weeks. Thus it is evident that in both the normal and immune-allergic animals with ocular tuberculosis, the degree of ocular inflammation resulting from infection closely parallels the degree of ocular sensitivity. The ocular inflammation

* The tuberculin used for the determination of ocular sensitivity was the purified protein derivative of Seibert, known as P.P.D.

resulting from the infection likewise increased and paralleled the ocular sensitivity to tuberculin.

In the second experiment (Study VI), a group of immune-allergic rabbits was divided into three sub-groups A, A[1], and B. Prior to inoculation of the eyes, the A rabbits were desensitized with tuberculin, and in order to maintain desensitization, the tuberculin treatment was continued after the anterior chamber inoculation. The A[1] rabbits were partially desensitized, and were given no tuberculin after ocular inoculation. The B rabbits were not treated with tuberculin at any time.

The course of the ocular inflammation in these three groups of rabbits is shown in Fig. 5, the ordinates expressing the degree of inflammation, and the abscissae the elapsed time in weeks. The desensitized A rabbits showed no initial reaction in the eyes to the tuberculo-protein in the inoculum, and later developed a

FIG. 5.

Average ocular activity of reacting rabbits of groups A, A[1] and B.

restrained ocular tuberculosis of low degree. Only at the end of the eighteenth week, when the disease was beginning to subside in all three groups, did the clinical inflammation of the desensitized A rabbits approximate that of the other two groups. On the other hand, both the partially desensitized A[1] rabbits, and the hypersensitive B rabbits showed a marked degree of reaction to the tuberculo-protein in the inoculum, and both groups showed more severe inflammatory reactions in the eyes than did the desensitized rabbits.

Thus it appears that the influence of tissue allergy on the resulting tuberculous lesion is substantiated for ocular tuberculosis. In both normal and immune-allergic rabbits, infected in the eye with the minimal dose of bacilli capable of producing constant symptoms, the ocular inflammation, necrosis and caseation, parallel the degree of ocular sensitivity. In immune-allergic rabbits, with an initial high ocular sensitivity, the immediate ocular inflammation is severe, and so remains. In similar rabbits with an initial low ocular sensitivity, the ocular inflammation is low at first, and only develops as the ocular sensitivity increases. Desensitization prior to inoculation abolishes the primary ocular reaction to

tuberculo-protein, and the ocular inflammation resulting from inoculation of the eyes is of low degree when the desensitized status is maintained.

C. *The influence of immunity on the ocular lesion.* The degree of immunity existing in the various immune-allergic animals was not uniformly quantitated by the injection of living bacilli in the skin, and clinical and histological examination of the resulting reaction. In the early experiments this was done in a number of rabbits, but no noteworthy differences in the reaction were observed, and the procedure introduced the element of possible changes produced by a second infection. The information on the rôle of immunity on the ocular lesion, as evidenced by these experiments, may be summarized as follows.

First, the minimal dose of bacilli which produces marked ocular disease in the normal rabbit, has no effect when introduced in the eye of a rabbit recovered from a prior systemic infection (Study III). The rabbit has developed a resistance to re-inoculation. Second, it requires approximately fifty times this dose to produce tuberculous disease in the eyes of immune-allergic rabbits, the amount varying in different animals. In a small percentage of immune-allergic rabbits, no ocular disease resulted from the standard fifty-fold dose. Third, this resistance to re-inoculation is only relative. If enormous doses are given, it is immediately overwhelmed, and violent inflammatory symptoms develop (Study VI). Fourth, this resistance to re-inoculation is totally undisturbed by complete desensitization of the rabbits prior to inoculation (Study VI). It still requires the same increased dose to produce ocular lesions, as compared with the normal rabbit. In fact, in this experiment, the desensitization appeared actually to favour the action of the immunity, the desensitized group showing a slightly higher incidence of complete immunity, and a decided increase in the incubation period—seven weeks as compared to two weeks in the sensitive controls.

There is therefore considerable confirmation for the influence of immunity on the tuberculous lesion in the eye. The course of the ocular disease is radically different in normal animals with no immunity, and in immune-allergic animals with immunity from a prior infection. While the degree of immunity resulting from a prior infection may be variable, it always requires a much higher dose of bacilli to produce tuberculous lesions in the previously infected animal than it does in the normal animal. Immunity functions entirely independently of sensitivity, and indeed in these experiments appeared somewhat enhanced when sensitivity was removed.

D. There remains one last point to be discussed in this connection—the puzzling question of why certain experimental animals, and likewise clinical patients with ocular tuberculosis, show a low degree of cutaneous reactivity to tuberculin, when the clinical appearance of the eye would indicate a high degree of tissue sensitivity.

This was investigated by simultaneous estimations of the cutaneous and ocular reactivity to tuberculin (*a*) in systemically infected animals without ocular disease, (*b*) in normal animals infected with tubercle bacilli in the eye, and (*c*) in immune-allergic animals secondarily infected in the eye.

Fig. 6 illustrates the general parallelism between ocular and cutaneous sensitivity in systematically infected animals without ocular disease (Study I). While there were wide fluctuations, in

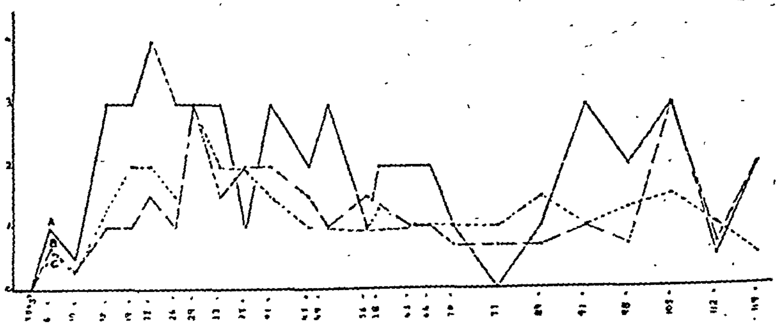

FIG. 6.

Curves showing the parallelism of ocular and cutaneous sensitivity in the systemically infected rabbits. Curve A represents the cutaneous sensitivity; curve B the clinical ocular sensitivity. and curve C the histological ocular sensitivity.

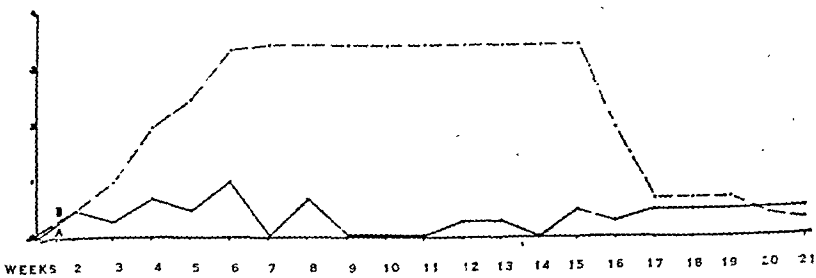

FIG. 7.

Curves showing the relation of the ocular sensitivity to cutaneous sensitivity in the normal rabbit after inoculation of the anterior chamber with tubercle bacilli. Curve A represents the cutaneous sensitivity, and curve B the ocular sensitivity.

general the cutaneous and ocular sensitivity paralleled each other. The most marked fluctuations occurred in the cutaneous sensitivity, when hot weather appeared to increase the cutaneous reactivity.

Fig. 7 represents the relation of ocular reactivity to tuberculin to cutaneous sensitivity in normal animals inoculated in the eye with tubercle bacilli (Study III). As the bacilli propagate and spread through the eye, intense local reactivity to tuberculin develops which only subsides when the process burns out. The cutaneous reactivity to tuberculin is only slightly stimulated by the local disease process in the eye. In short, in the otherwise

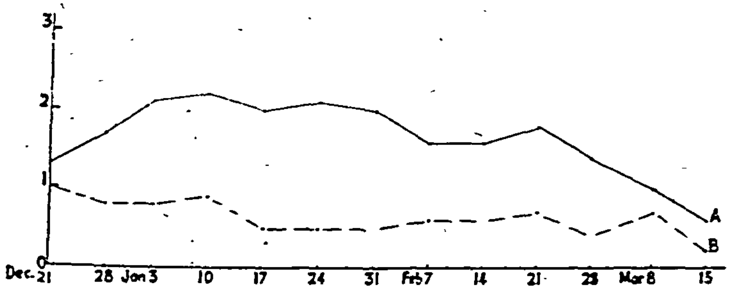

FIG. 8.

(Experiment 1)—Relation of ocular sensitivity (A) and cutaneous sensitivity (B) after intra-ocular injection of tubercle bacilli in immune-allergic rabbits.

normal animal with local ocular tuberculosis, the cutaneous reactivity to tuberculin is no index of the ocular reactivity.

Fig. 8 shows the relative ocular and cutaneous reactivity to tuberculin in immune-allergic rabbits infected in the eye with tubercle bacilli (Study IV). At the time of inoculation the ocular and cutaneous sensitivity were about the same, as would be expected. As the bacilli spread slowly throughout the eye, there was a concomitant slow rise in the local ocular reactivity or sensitivity. The ocular sensitivity began to decline slowly at the end of the ninth week, as the local disease subsided. The cutaneous sensitivity, however, was not affected by the local ocular disease, and over a three-month period slowly declined and faded.

These experiments offer an explanation for the relative cutaneous anergy sometimes observed in ocular tuberculosis with acute inflammation. If there is local tuberculous disease in the eye there is no necessary relation between the ocular reaction to the products of the tubercle bacillus and the cutaneous sensitivity. If the cutaneous sensitivity is high, the ocular sensitivity is also high,

for the eye partakes of the general systemic sensitivity. However, local disease in the eye may produce a high degree of ocular sensitivity to tuberculin, while it does not influence or affect a normally low cutaneous sensitivity. In other words, if the cutaneous sensitivity is low, it does not necessarily imply that the ocular sensitivity is also low. The latter may be high or low, depending on the presence and extent of an ocular tuberculosis. Whether the increased ocular reactivity to tuberculin is the result of an increased vascularity produced by the local disease, or is a true selective local sensitization, is largely an academic question which need not concern us here.

It seems reasonable to conclude from these experiments that the principles involved in Rich's law, laid down for systemic tuberculous lesions, also hold good in localized ocular tuberculosis without active systemic lesions. It is further evident that the determination of the cutaneous reactivity to tuberculin does not always give an accurate picture of the local ocular reactivity. If cutaneous sensitivity is low or absent, and there is tuberculous disease in the eye, the ocular reactivity to the products of the tubercle bacillus may still be high.

II.—THE TREATMENT OF EXPERIMENTAL OCULAR TUBERCULOSIS

A. *The Enhancement of Immunity.* In 1893 Trudeau stated that the achievement of a complete artificial immunity in tuberculosis was an ideal never likely to be attained. Unfortunately that is still largely true today. It has already been pointed out that as a result of a prior infection, the rabbit acquires a well marked resistance to re-inoculation. This well known fact has been employed in the mass inoculation of children with the attenuated B.C.G. organism, and the results have been somewhat gratifying in the lessened incidence of tuberculosis in the inoculated group. This lengthy procedure is, however, a far cry from the artificial stimulation of an immunity calculated to benefit an already existing infection. While we have done little work on this problem, and the little we have done has been quite barren of any results, one observation has been made which may be of some academic interest.

It was noticed that in immune-allergic rabbits with a secondary ocular tuberculosis, the clinical evidences of inflammation and activity might entirely subside while there was still a low degree of demonstrable sensitivity in the affected eye, and that these eyes did not develop further tuberculous disease when given a second injection of bacilli shortly after the subsidence of symptoms (Study VI). It was thought at first that this might be due to an exhaustion

of the reactive capacity of the eye, but this supposition was proven untrue, since the eyes reacted quite briskly to other non-tuberculous stimuli and infections. It was then supposed that this phenomenon might be due to an increase in the general immunity brought about by the recent ocular disease from which the animal had recovered. This supposition was also untenable, because it was found that the second undiseased eyes of these same rabbits reacted quite promptly to the injection of the proper dose of bacilli (Study VI). Another possible explanation was that this healing and immunity to re-inoculation might be due to the increased vascularity produced by the ocular disease, thus rendering the humoral element of the general immunity more efficacious. Experiments (Study VIII) in immune-allergic rabbits with eyes vascularized by other non-tuberculous infections, revealed that increased vascularity was not in itself the dominant factor in this resistant state, and indicated some mechanism other than humoral immunity.

Continued study of these apparently immune eyes revealed the fact that the local immunity was only transitory, that spontaneous recurrences of the inflammation occurred in 25 per cent. of such rabbits within a year, and within this same time the remaining 75 per cent. lost their immunity, and these eyes developed a further attack of ocular tuberculosis on re-inoculation (Study VIII). Further, the histological examination of eyes recently recovered from an attack of tuberculosis, and presumably immune to re-inoculation, revealed definite sub-clinical areas of infection with epithelioid cells and macrophages. Examination of similar eyes a year later, when they were again theoretically susceptible to re-inoculation, showed that the epithelioid cells and macrophages had largely disappeared.

On the basis of these observations it was concluded that the transient immunity to re-inoculation shown by eyes recently clinically recovered from tuberculosis was due not to a humoral immunity, but to the persisting mobilization of macrophagic cells. In short, whatever might be the rôle of the circulating anti-bodies in immobilizing and fixing the bacilli, the *sine qua non* in this local resistant state appeared to be the presence of macrophagic cells.

The obvious method of testing this hypothesis was the pre-mobilization of macrophagic cells in the eye prior to the introduction of the infecting bacilli. This we attempted to do by the local injection of tuberculo-phosphatides in the anterior chamber, and finally in the stroma of the ciliary body.

This experiment, previously unreported, was completely inconclusive. When phosphatides were introduced into the anterior

chamber, they were apparently immediately excreted, and the eyes on section showed no cellular response. When the phosphatide was injected in the ciliary stroma, there ensued a clinical inflammatory reaction, and histologically an outpouring of epithelioid cells and macrophages. When such eyes were later injected with tubercle bacilli and compared with controls, it was difficult to differentiate with any certainty the tuberculoid lesions caused by the phosphatides and true tubercular lesions produced by the living bacilli. The intra-ocular injection of phosphatides did not appear to be a happy experimental approach to the problem. Thus these efforts to enhance the local resistant state have been fruitless.

B. *The Effect of Desensitization on Experimental Ocular Tuberculosis.* Prior to Rich's paper in 1929, it was generally supposed that allergy and immunity were inter-dependent, and that by evoking an allergic reaction, immunity might be stimulated. This was the idea underlying the therapeutic use of tuberculin in localized tuberculosis—namely to evoke sub-clinical allergic reactions and thus stimulate immunity. This was known as the perifocal concept. Rich's demonstration of the independence of allergy and immunity introduced at once the new therapeutic concept of removing the fatal tissue hypersensitivity by desensitization with tuberculin. Thus tuberculin would be given sub-cutaneously with the idea of avoiding all clinical or sub-clinical focal reactions, and the dose would be increased only as the point of reactivity receded. By this means tissue desensitization would be finally accomplished. However, it is quite true that either clinical or sub-clinical reactions will produce some desensitization, in that they deplete the local antibody reservoir. The value of avoiding focal reactions is therefore to obviate the local destructive effect such focal reactions necessarily entail.

In experimental work with rabbits, it is impracticable to employ the long-drawn-out process of desensitization with the small doses of tuberculin one would use in humans. Rabbits are not the happiest animals to use for desensitization experiments with tuberculin. They do not become hypersensitive as readily as guinea-pigs, they tolerate huge doses of tuberculin somewhat better than guinea-pigs and vastly better than humans. Lastly, since the ocular disease naturally runs a self-limiting course of from three to six months, it is necessary to accomplish desensitization rapidly in order to evaluate any observed therapeutic results. In the experiment to test the effect of desensitization on an already existing ocular tuberculosis in the immune-allergic rabbit, tuberculin was therefore administered subcutaneously in the large dose of 100 mgms., or (0·1 c.c.) of old tuberculin twice weekly. While a

focal reaction was observed following the first dose, this reaction was evanescent and did not produce any ocular damage. That this focal reaction was not responsible for the therapeutic effect was demonstrated by the observation that a precisely similar focal reaction had no effect on the hypersensitive controls which were not maintained in a state of desensitization.

The essence of this experiment (Study VII, was to prepare a large series of immune-allergic rabbits with secondary ocular tuberculosis. As soon as the ocular disease was established clinically, the rabbits were divided into two groups of equal severity. One group was untreated, while the second group was treated with tuberculin. The clinical course of the two groups was followed, and various minor tests were made during the course of the experiment to determine the progress of desensitization.

The results of this experiment are shown graphically in Fig. 9. After the inoculation of the eyes with tubercle bacilli there was an immediate reaction in the eyes to the tuberculo-protein in the inoculum. This rapidly subsided, and well-marked tuberculous lesions in the eyes were present by the third week, when the rabbits were divided into two groups of equal severity. Tuberculin was then started in one group. There was an immediate focal reaction in the eyes which subsided within one week. Thereafter the severity of the disease in the treated group, which continued to receive the desensitizing injections, rapidly subsided as compared with the untreated group, and at the end of the twelfth week, this difference in the two groups was marked. As the experiment progressed to the twenty-fourth week and the ocular disease in the control group naturally burned out, the picture in the two groups approximated each other. Various minor tests, the determination of ocular reactivity in the control group, the determination of the relative ocular sensitivity of sample pairs from the two series, the estimation of the ocular and cutaneous sensitivity at the end of the experiment, all indicated that the observed clinical improvement in the treated group paralleled their desensitization to tuberculin. Indeed, there was some evidence that there was a selective desensitization of the eyes, which might be expected, since it is known that tuberculin is a fine colloid and tends to filter out at the site of local inflammation.

The ultimate fate of the desensitized rabbits is interesting, and may be of importance in planning the method in which tuberculin should be used clinically. At the completion of the experiment the treated rabbits showed a degree of cutaneous sensitivity so low that the animals were practically insensitive. One year later, after cessation of treatment, the sensitivity had returned, and the animals showed a high degree of both ocular and cutaneous sensitivity.

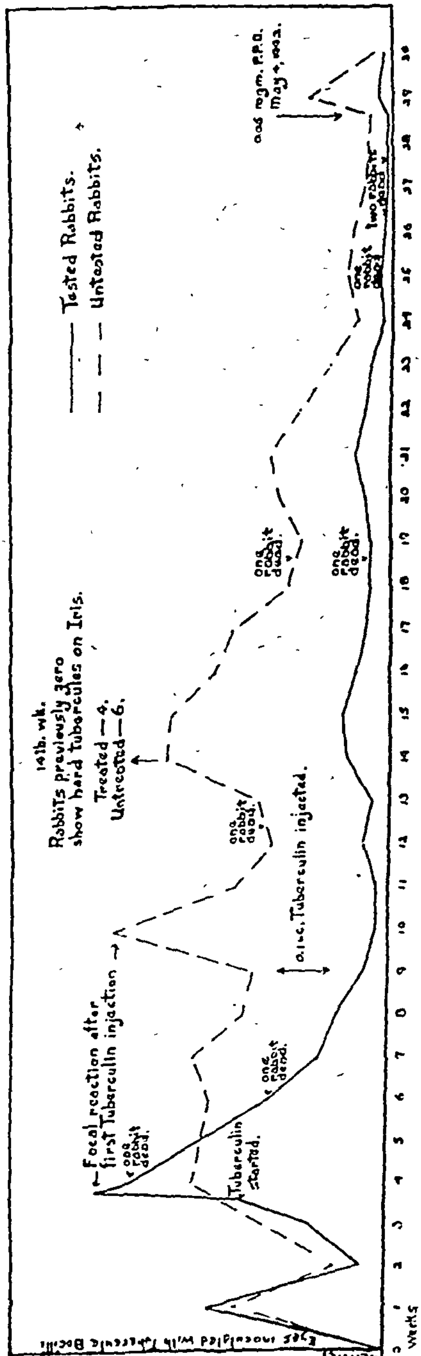

FIG. 9.

Effect of treatment on ocular tuberculosis in immune-allergic rabbits.

Synchronous with the return in sensitivity, there had been a disastrous ocular recurrence in 36 per cent. of the rabbits.

The conclusions to be drawn from this experiment appear clear. Desensitization with tuberculin is accompanied by a marked decrease in the clinical inflammatory manifestations of the disease, and exerts a thoroughly beneficial effect. It does not cure the disease in the sense of destruction of the bacilli, or even of bacteriostasis. It merely removes the factor responsible for the destructive phases of the lesion. If tuberculin treatment is terminated, the fatal tissue sensitivity recurs, and coincident with its return in a large percentage of the animals, there is a recurrence of the ocular inflammation.

C. *The effect of chemotherapy and antibiotics in ocular tuberculosis.* Prior to 1940, no therapeutic agent had been found with any marked specific deterrent action on the tubercle bacillus. It is true that Koch had observed the inhibitory action of colloid of gold salts on the *in vitro* growth of tubercle bacilli, but their clinical use had given no spectacular results, and the untoward effects were so severe that their use has been almost completely abandoned. Efforts had been made to treat tuberculosis with various dyes combined with metallic salts of bactericidal action. The thought behind such treatment was the known ability of such dyes to penetrate tubercles. The clinical results were, however, not encouraging. Some hope was later aroused by the demonstration that sulphanilamide used prior to inoculation had an inhibitory effect on the later development of tuberculosis in guinea-pigs. However, sulphanilamide had no effect in tuberculosis when used clinically. It was not until 1940, when Feldman and his co-workers showed the deterrent action of certain diamino-diphenyl sulphones in experimental tuberculous lesions, that there was any real demonstration of an effective chemo-therapeutic agent in tuberculosis. These sulphones were known as diasone, promin and promizole. Diasone was relatively toxic and therefore of little value. Promin was moderately toxic, while promizole was relatively non-toxic. In fact, promizole can be administered to humans up to 12-15 grams daily with comparative safety.

The first step in the study of chemo-therapy of ocular tuberculosis was to determine the effects of promin and promizole in both normal and immune-allergic rabbits with ocular tuberculosis. The drugs were administered in food in 1·0 per cent. concentration over a four-month period. The daily dose was approximately 1·5 gm., which produced a blood level ranging around 2·0 mgm. per cent. The results of this treatment in normal rabbits (Study XI) are shown in Fig. 10, where the course of the disease in the treated animals is compared with untreated controls. There was

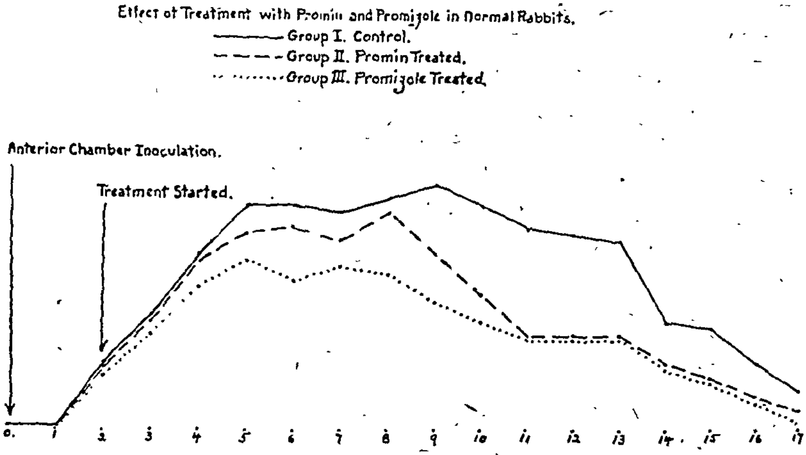

FIG. 10.

Effect of treatment with promin and promizole in normal rabbits.

a slight, but statistically insignificant, relative decrease in the disease in the treated animals at the end of the second week, and a slightly more significant decrease at the end of the eighth week. However, at the end of the twelfth week, the majority of the eyes in both the control and treated groups had gone into buphthalmos and ruptured. There was only a slight advantage in favour of the treated groups. There was little difference in the histological picture, and on transmission experiments from the diseased eyes the uveal tracts of both the treated and untreated groups were all infectious. It was concluded therefore that promin and promizole had only a very slight deterrent action on ocular tuberculosis in the normal animal.

The results of treatment in immune-allergic rabbits were much more striking. These results are shown in Fig. 11. After three

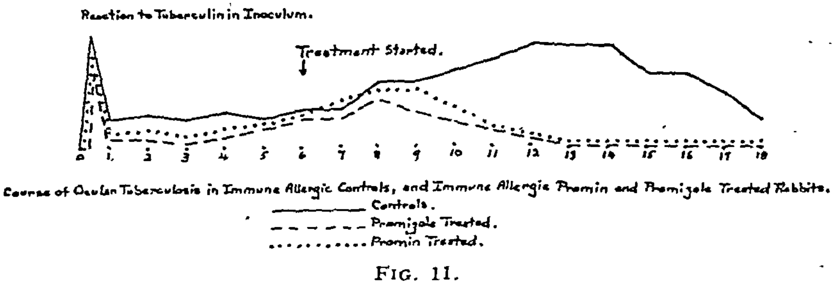

FIG. 11.

Course of ocular tuberculosis in immune-allergic controls and immune-allergic promin and promizole treated rabbits.

weeks' treatment, the treated animals began to improve, while the disease became more severe in the untreated controls. At the end of the fourteenth week, when the disease in the controls was at its maximum, the eyes of the treated rabbits were almost completely inactive. At the end of the sixteenth week, the eyes of all the treated animals were entirely quiet on clinical examination, while 80 per cent. of the controls still showed active inflammation. The histological examination, however, was not so conclusive. Of the treated rabbits sacrificed for histological study, approximately 50 per cent. showed small, persisting areas of active tuberculosis, while the remainder showed only scarring. There was no statistical difference between the promin- and the promizole-treated animals. On transmission experiments, under the technique used in this experiment, only one of the treated animals showed an infectious uveal tract, while all the controls were positive.

It was concluded from this experiment that both promin and promizole had a marked deterrent action on ocular tuberculosis in the immune-allergic rabbit, but this action was not absolute in the sense of producing a complete destruction of the tubercle bacilli. In the light of the negative experiment in normal rabbits it was suggested that this deterrent action might be due either to a degradation or attenuation of the virulence of the organisms, allowing the resistance of the host to become more active, or to a partial bacteriocidal action, bringing the infection within the range of the host's resistance.

The next step in the search for agents with a deterrent action on the lesions of ocular tuberculosis was obviously to explore the effect of the antibiotics. Although Abraham, Chase and Florey had reported as a result of their *in vitro* experiments that the tubercle bacillus was insensitive to penicillin, nevertheless the literature was singularly barren of conclusive evidence that this was true *in vivo*. Such experiments as were reported were all open to the criticisms that the dosage was insufficient, or the number of animals too few to validate any conclusion. It seemed, therefore, worth-while to investigate the question further.

Normal rabbits, injected in the eye by the usual anterior chamber injection, were used (Study IX). This was admittedly a severe test. Sixteen rabbits were treated with penicillin, 200,000 units per diem, in divided doses, for a period of 45 days. An equal number of similarly infected, but untreated, rabbits served as controls. The results of this experiment are shown in Fig. 12. The clinical course of the treated and untreated rabbits was identical. Penicillin had no effect whatsoever on the clinical lesions. Histological examination of the treated and untreated eyes showed slightly less tuberculous disease in the treated eyes,

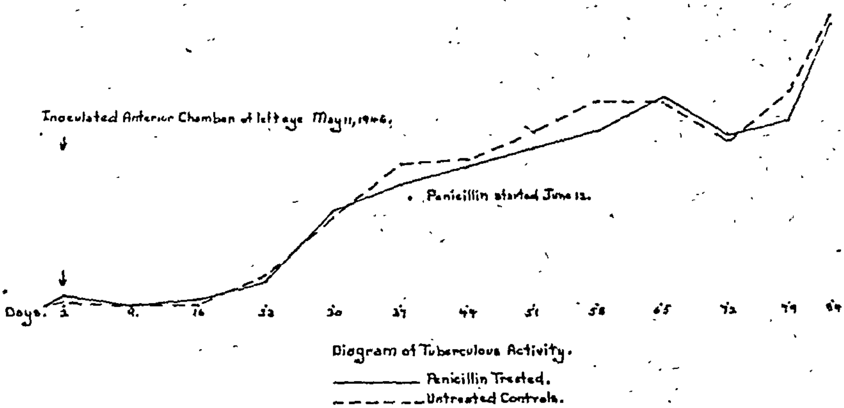

FIG. 12.

Diagram of tuberculous activity in controls and penicillin treated rabbits.

but when this was subjected to statistical analysis it was found to be without significance. It was concluded that penicillin was without action in ocular tuberculosis under the conditions of this experiment.

The last experiment performed was on the action of streptomycin alone, and of streptomycin combined with promizole (Study XII). This experiment was done in immune-allergic rabbits. Inasmuch as the same untreated group served as controls in both the streptomycin alone and the streptomycin plus promizole treated rabbits, these two experiments are shown together. Streptomycin was given in both the treated groups in the dosage of 50 mgms. per kilo of bodyweight per diem, in one dose, and promizole in the dose before outlined, about 1·5 gms. per diem. These dosages gave blood plasma levels up to 7·6 mgms. per cent. for streptomycin, and an average of 1·7 mgms. per cent. for promizole. The period of treatment was two and a half months. The number of rabbits in each group (controls, streptomycin-treated, and streptomycin-*plus*-promizole-treated) was approximately 20 each.

The results of this experiment are shown graphically in Fig. 13. In both treated groups the results were dramatic. At the end of the second week of treatment, there was a marked difference in favour of the treated groups. At the end of the fourth week this change was striking. The control group had a level of " 2 " for the ocular inflammations, while the treated groups were almost quiescent clinically, the average being 0·25. While the charted averages of activity are practically identical in the two treated groups, the improvement was much more marked in the group

FIG. 14.

Control—February 25—maximum reaction

FIG. 15.

Control—April 28—maximum reaction.

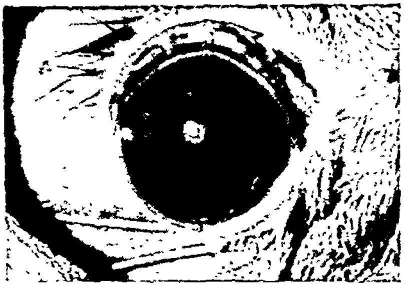

FIG. 16.

Control—February 25—minimum reaction.

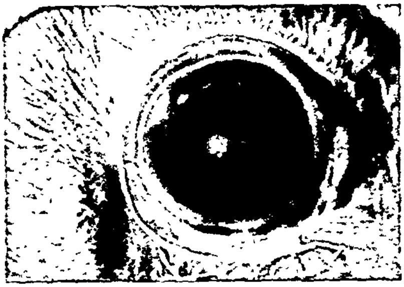

FIG. 17.

Control—April 28—minimum reaction.

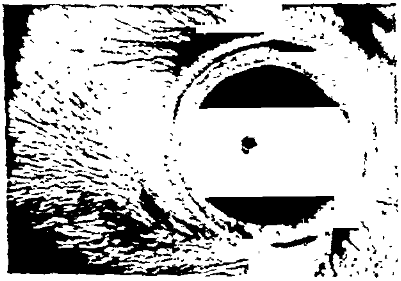

FIG. 22

Streptomycin-treated—before treatment.

FIG. 23.

Streptomycin-treated—after treatment.

FIG. 24.

Streptomycin-treated—before treatment.

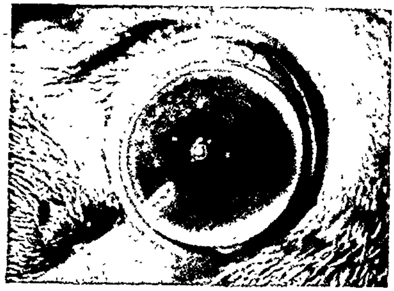

FIG. 25.

Streptomycin-treated—after treatment.

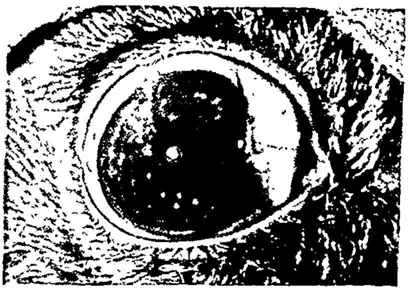

FIG. 30.

Streptomycin-plus-promizole-treated rabbit—before treatment.

FIG. 31.

Streptomycin - plus - promizole - treated rabbit—after treatment.

FIG. 32.

Streptomycin - plus - promizole - treated rabbit—before treatment.

FIG. 33.

Streptomycin - plus - promizole - treated rabbit—after treatment.

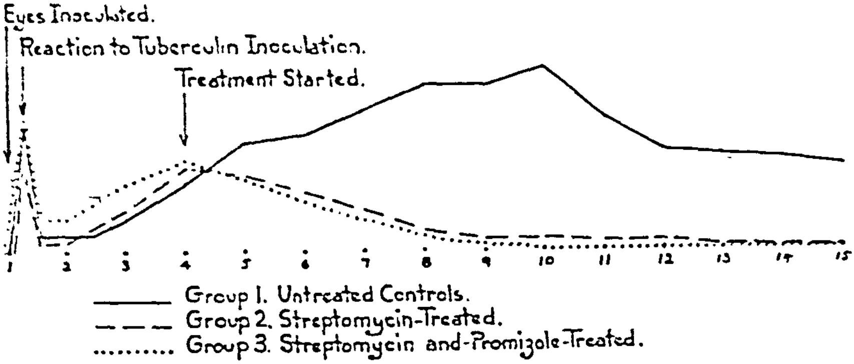

FIG. 13.

The effect of streptomycin alone and streptomycin plus promizole in the immune-allergic rabbit.

treated with the combination of streptomycin and promizole. One apparently non-immune rabbit with a severe and resistant ocular tuberculosis accounted for the greater portion of the activity in the streptomycin-promizole group. The lesions in this rabbit subsided only after twelve weeks of treatment.

The differences in the histological pictures were equally striking. The rabbits of the control group sacrificed for histological study all showed numerous hard tubercles throughout the cornea, iris and ciliary body together with monoculear and epithelioid cell infiltration. The rabbits treated with streptomycin alone showed minimal lesions only. The rabbits treated with a combination of streptomycin and promizole showed no active lesions, the sections showing only scarring, an occasional encapsulated tubercle, and persistence of wandering cells in the iris and ciliary body.

The different clinical course and histological pictures can well be demonstrated pictorially. Thus Figs. 14 and 15, and Figs. 16 and 17, show the high and low extremes in the control group, at the onset of inflammation and at the end of the experiment. Figs. 18-19 show the typical histological picture of untreated tuberculosis in these same control immune-allergic rabbits. Figs. 18-19 illustrate the maximum histological reaction, while Figs. 20-21 illustrate the minimum histological reaction. Figs. 22-23, and Figs. 24 and 25, show the before and after clinical pictures of typical rabbits treated with streptomycin alone, and Figs. 26-29 show the minimal histological lesions in these same rabbits. Figs. 30-31, and Figs. 32-33, show again the before and after clinical pictures of typical rabbits treated with the combination of streptomycin and promizole, and Figs. 34-38, show the total absence of any active histological lesions in these same animals, the evidences of tuberculosis being limited to an encapsulated tubercle and the persistence of wandering cells.

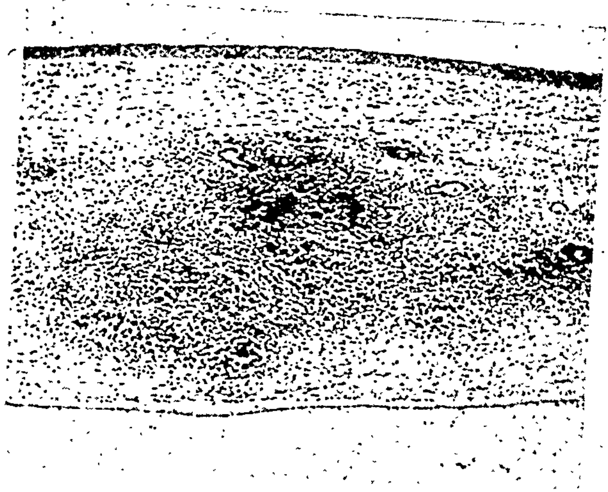

FIG. 18.

Cornea of control rabbit—maximum reaction.

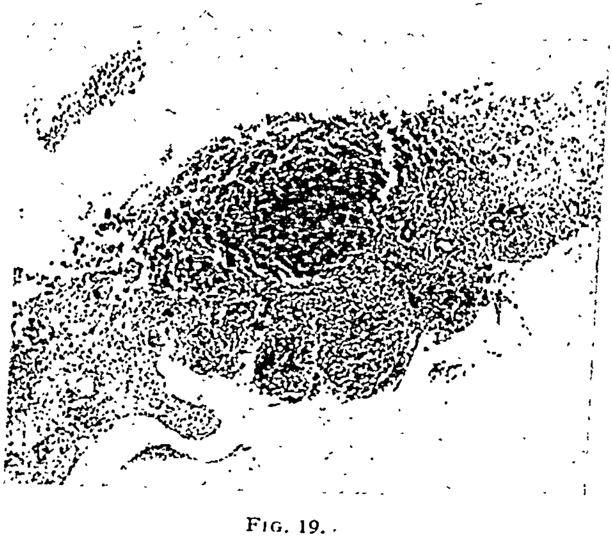

FIG. 19.

Iris of control—maximum reaction.

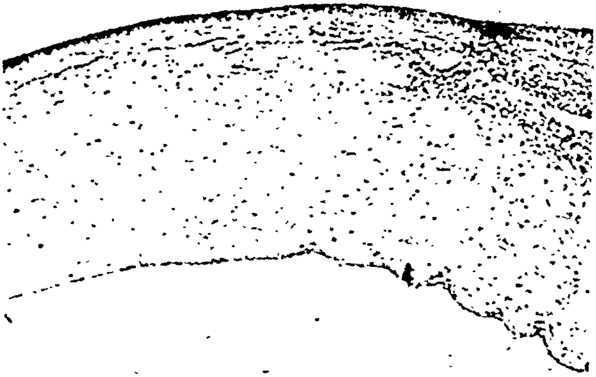

FIG. 20.

Cornea of control—minimum reaction.

FIG. 21.

Ciliary region of control—minimum reaction.

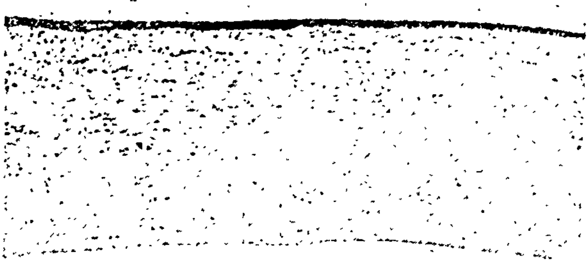

FIG. 26.

Cornea of streptomycin-treated rabbit—minimal infiltration.

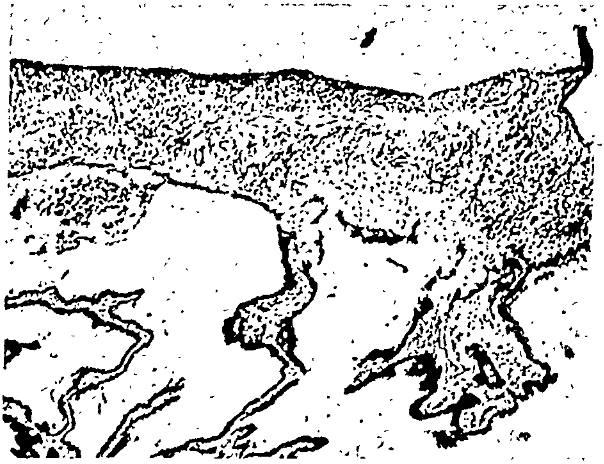

FIG. 27.

Iris of streptomycin-treated rabbit—small tubercle on posterior surface. Healed tubercle in stroma

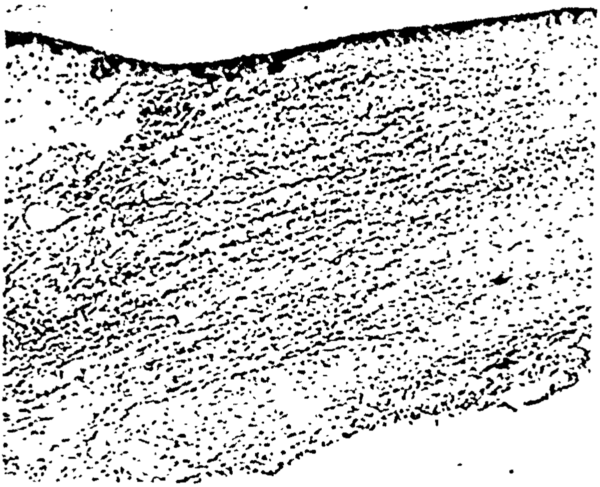

FIG. 28.

Cornea and root of iris of streptomycin-treated rabbit—minimal infiltration.

FIG. 29.

Root of iris and ciliary body of streptomycin-treated rabbit—moderately intense infiltration.

FIG. 34.

Streptomycin-plus-promizole-treated rabbit—minimal scarring.

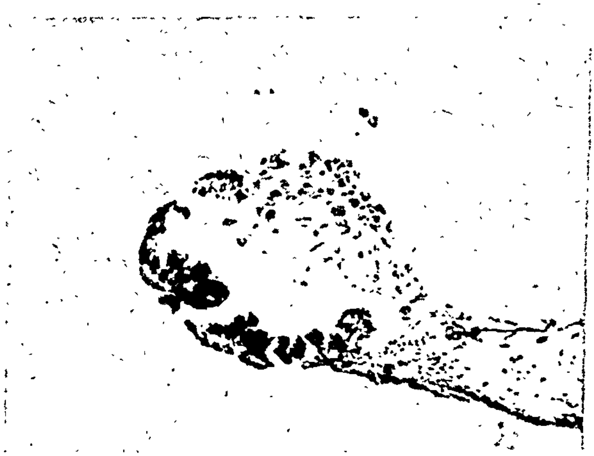

FIG. 35.

Streptomycin-plus-promizole-treated rabbit—healed tubercle at tip of iris.

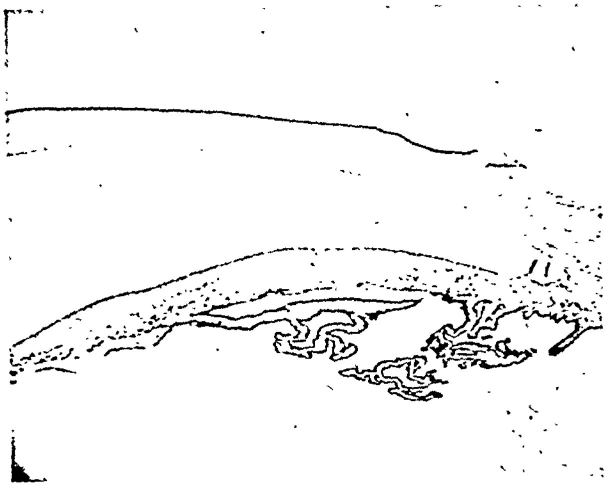

Fig. 36.

Streptomycin-plus-promizole-treated rabbit — normal anterior ocular segment

Fig. 37.

Streptomycin-plus-promizole-treated rabbit—minimal scarring of iris, persistence of wandering cells.

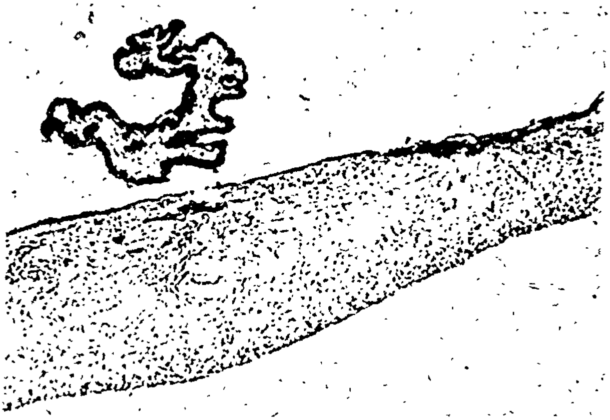

FIG. 38.

Streptomycin-plus-promizole-treated rabbit — showing persistence of wandering cells in iris.

At the conclusion of the therapy, six rabbits in each grou were sacrificed for histological study, six others for culture of th dissected-out uveal tracts and for transmission experiments, and th remainder kept under observation for any recurrences of inflan mation. The transmission experiment in these rabbits was a muc more severe test than that employed in the previous experimer for rabbits treated with promin and promizole alone. The dissecte uveas were macerated in only 1·5 c.c. of salt solution, wherea 5·0 c.c. of dilutant had been used in the experiment with promi and promizole alone. The results of these culture transmissio experiments, and the incidence of recurrences in the survivin rabbits are shown in Table I. Thus the cultures of all control were positive, showing from 15 to innumerable colonies in eacl slant. In the rabbits treated with streptomycin alone, three culture were positive with 1-3 colonies only, while three were negative. Ir the rabbits treated with streptomycin and promizole, five culture were entirely negative, while the sixth culture showed no macro- scopic colonies, but bacilli were found on microscopic examination.

On transmission experiments, all the uveal tracts of the control group were infectious. In both the streptomycin-treated rabbits and the streptomycin-promizole-treated rabbits, 50 per cent. of the uveal tracts were infectious, and 50 per cent. non-infectious.

Recurrences occurred in three out of nine surviving rabbits treated with streptomycin alone, the average remission period

	Transfer		Cultures of Uveal Extracts		Recurrences	
	Results	Incubation Period	Results	Incubation Period	Results	Remission Period
Group I (untreated controls)	100% positive.	17 days	100% positive	Heavy growth in 4 weeks.	gradually waning activity.	
Group II (Streptomycin alone)	50% (3) positive. 50% (3) non-infectious.	26 days	50% (3) positive for tubercle bacilli 50% (3) neg	1-2 colonies in 5 weeks.	3 out of eight (37%)	12 days (average)
Group III (Streptomycin + Promizole)	50% (3) positive. 50% (3) non-infectious.	33 days	83% (5) negative. 17% (1) positive.	microscopic growth in one culture only in 8 weeks.	1 out of nine (11%) (minimum reaction)	34 days

TABLE I.

Results of transfer experiments and cultures and incidence of recurrences

being 12 days. In the streptomycin-promizole treated rabbits, there was one recurrence in nine rabbits, the remission period being 34 days. Resistance experiments on the recovered organisms are as yet incomplete.

From these studies on the action of sulphones and antibiotics in ocular tuberculosis, it is conservative to conclude that a relatively non-toxic sulphone, promizole, has a deterrent action on the local tuberculous lesion in the immune-allergic rabbit. The deterrent action is far from absolute, and at best is scarcely more than sufficient to restrain the growth of the bacilli, or attenuate their virulence, to within the bacteriostatic or bactericidal range of a fairly well-developed immunity. Streptomycin has a much more powerful therapeutic action, undoubtedly a true bacteriocidal action, but again, as administered in these experiments, this action is not always absolute. The combined action of streptomycin and promizole is much more pronounced, and appears to eradicate the bacilli from the infected tissues in a large percentage of the treated cases, and certainly to curtail their growth and virulence in the remaining cases.

SUMMARY

These experimental findings may be summarized as follows: It appears that Rich's law for the pathogenesis of tuberculous lesions holds true in localized ocular tuberculosis. The factors governing the course and character of the lesion are the number and virulence of the infecting organisms, the degree of tissue hypersensitivity present, and the amount of the resistance established by the host. These studies also offer an explanation for the

relative cutaneous anergy often present in animals and man with inflammatory tuberculous lesions of the eye.

This concept of the pathogenesis of a tuberculous lesion offers obvious points for therapeutic attack on the disease. The first of these is enhancement of immunity, and nothing specific has been done as yet to stimulate local resistance artificially. The second is removal of the fatal tissue hypersensitivity, and this can usually be accomplished by the use of tuberculin as a desensitizing agent, and has a distinctly beneficial effect on the clinical course of the lesion. The third is the direct attack on the tubercle bacilli, and in streptomycin and promizole combined, we have a powerful weapon to this end. Doubtless other better antibiotics and sulphones will be found, but at present this combination appears the best available.

THE VASCULAR ACTION OF PILOCARPINE, ESERINE ADRENALINE AND ATROPINE, AND THEIR INFLUENCE IN PRIMARY CHRONIC GLAUCOMA*

BY

G. CRISTINI

BOLOGNA

THE rationale of the action of miotic and mydriatic drugs in glaucoma is a matter which still retains its importance, not only because our knowledge of the mechanism of the action of these drugs is still incomplete, but also because the discovery of new antiglaucomatous drugs and modern researches on the chemical mediation of the transmission of nerve impulses have amplified the problem without offering any substantial explanation. Moreover, the interpretation of the mechanism of these drugs—still an unsolved problem when they act upon the normal eye—becomes more complicated when they are considered in relation to the added problems involved in the development of a raised intra-ocular pressure in glaucoma.

In physiological literature we find the most diverse views regarding their effect on the ocular tension and the vascular system in the eye. Without mentioning Leber's notes in "Graefe Sämisch Handbuch," but reviewing the opinions of recent authors only, we find that in Colombo's opinion eserine and pilocarpine cause vasoconstriction, whereas Bailliart and Bidault attribute to

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these same drugs a vasodilatory influence, particularly marked and visible in the conjunctival vessels; Michail and Vancea are in agreement with them. In Wessely's opinion eserine causes vasoconstriction in the conjunctival vessels and vasodilatation in the vessels of the iris and the ciliary body. Dieter and Thiel, on the ground of experimental findings, also suggest that these drugs cause a vasodilatation. Koellner, in a case of persistent pupillary membrane in man, was likewise able to observe a vasodilatation. Atropine, according to Colombo, causes vasodilatation as also does cocaine, a view with which Michail agrees; while according to Bailliart and Dieter, the action of this drug is vasoconstrictive. Among the most exhaustive physiological researches on this subject are those of Colle, P. M. Duke-Elder and W. S. Duke-Elder. On the basis of direct observation of the vessels of the iris, the registration of contractions of the extra-ocular muscles, temperature records taken in the anterior chamber and the measurement of the intra-ocular pressure in healthy animals and in artificially perfused eyes, these authors reached the following conclusions with regard to the relations of muscle contraction, vasomotor action, size of the pupil and their influence on the ocular tension:

"Adrenaline in small doses dilates the capillaries, increasing their permeability and raising the intra-ocular pressure; in large doses it constricts the vessels, lowering the intra-ocular pressure; in any dose it stimulates the plain muscle of the orbit, raising the intra-ocular pressure, and dilates the pupil, which is without effect on the intra-ocular pressure.

"Atropine dilates the minute vessels and increases their permeability, thus raising the intra-ocular pressure, and relaxes the plain muscle of the orbit, thus lowering the intra-ocular pressure.

"Physostigmine dilates the small vessels and increases their permeability, and also increases the tone of the voluntary muscles of the orbit, thus increasing the intra-ocular pressure.

"'Pituitrin' constricts the arterioles, lowering the intra-ocular pressure, and stimulates the plain muscle of the orbit, raising the intra-ocular pressure.

"Histamine dilates the minute vessels and increases their permeability, raising the intra-ocular pressure, provided these have sufficient tone; otherwise its action is confined to a constriction of the arterioles, an action which lowers the intra-ocular pressure.

"Choline dilates the minute vessels and stimulates the voluntary striped muscles of the orbit, raising the intra-ocular pressure. Nicotine manifests its action entirely by stimulating the plain and striped muscle of the orbit to contract, thus raising the intra-ocular pressure.

"Curare lowers the intra-ocular pressure by relaxing the tone of the voluntary muscles."

On interpreting the action of these miotic and mydriatic drugs in glaucoma, however, all the hypotheses which have been advanced do not seem to fit in accurately with the results obtained with these physiological researches. Among the more popular hypotheses, Weber's is the most frequently quoted: the decrease in ocular tension determined by the use of miotic drugs in primary

glaucoma is due to a better outflow of the aqueous humour through Schlemm's canal resulting from the pulling away of the root of the iris from the posterior surface of the cornea. The prompt and, in some instances, considerable diminution of tension in cases of glaucoma with gross anatomical changes at the filtration angle, as in cases of *synechiae of the root of the iris with the posterior* surface of the cornea, or in cases where the canal of Schlemm is absent, as in hydrophthalmia, puts a limit to the validity of this hypothesis. Similarly, Hamburger's hypothesis, according to which miotic drugs favour the opening of the lymphatic pathways of the iris through an increase of the absorbing surface of this membrane, does not explain the diminution of ocular tension, particularly in those cases wherein the uveal tissue shows large areas of atrophy. The demonstration that the aqueous humour is very similar to a dialysate made the influence of the size of the pupillary diameter on ocular tension a matter of little importance (Duke-Elder). A further hypothesis among those commonly recorded is that of Kuesel and Fortin, by which it is suggested that the hypotensive effect of miotics is due to the contraction of the ciliary muscle by which not only are Fontana's spaces opened up owing to the pull on the scleral spur, but also the arterial inflow is reduced *in consequence of a compression of the long posterior* ciliary arteries as they traverse the muscular network of the ciliary body.

It seems peculiar that so little importance has been attributed to the purely vascular effect exerted by the miotic drugs: this action has been proved experimentally to be characteristic, and nowadays there can be little doubt that changes in the uveal circulation constitute one of the main causes of the development and rise of intra-ocular pressure in glaucoma. This, by the way, was the explanation offered regarding the effect of adrenaline in glaucoma, and it is now clear that this drug *acts merely by a modification* of the circulatory rate. Dieter is among the few who believe, without, however, giving a very clear explanation, that the effect of pilocarpine and eserine depends only on a simple vascular action. It is to be noted also that Thiel, who found experimentally a dilatatory influence of pilocarpine and eserine on the uveal vessels, is of the opinion that these drugs remove vascular stasis in glaucoma through a widening of the uveal vessels and an increased arterial " debit." He believes, however, that this action is not responsible for the entire effect and that further factors, such as a greater unfolding of the iris, are involved.

The problem of the action of miotics and mydriatics in glaucoma is substantially connected with the development and rise of intra-ocular pressure in this disease. In previous experimental

researches I have already formulated some considerations about the pathogenesis of this symptom, suggesting that one of the main causes is an alteration in the uveal circulatory " debit." For this reason, in the pfesent paper attention is drawn to the vascular action of the most common miotic and mydriatic drugs, analysing in particular their effect in glaucoma.

EXPERIMENTAL FINDINGS

The eyes of albinotic rabbits were studied and, in order to obtain experimental demonstrations of the vascular effects of adrenaline, pilocarpine, eserine and atropine on the iris, the ciliary body and choroid, the following techniques were adopted.

I

Watery solutions of 1 per cent. atropine, 2 per cent. pilocarpine, 0·5 per cent. eserine were instilled several times into the conjunctival sac of the experimental animals, and some drops of adrenaline in 1 : 1000 solution were injected under the conjunctiva. Subsequently, after half an hour, one, and two hours, when an intense miotic or mydriatic effect had appeared, the eyes were examined with the slit-lamp, the light from which was filtered through a chamber filled with copper sulphate solution and a Uviol filter. The vessels of the iris, which were of a black bluish colour in the filtered light, were examined through a corneal microscope (ocular 2, objectives 4 and 6 Zeiss).

From biomicroscopical examination, the following observations were made :

Adrenaline (Fig. I).

Both the circulus iridis major and the anterior arterioles branching radially from this circle were very thick and winding in comparison with the control eye. Near the pupillary border and, less dense, in the ciliary portion of the iris, one could, with strong magnification, make out the presence of a fine network of capillaries running parallel to the pupillary border. Contrary to Leber's findings, I could observe that this network, especially near the pupillary border, permits the formation of anastomoses between the terminal branches of the anterior arteries of the iris. Just above the pupillary border some small capillary arches were found that could likewise be observed in the control eye, although limited in number.

Pilocarpine and eserine (Figs. 5 and 8)

Observations with these two drugs are considered together because the biomicroscopic findings were analogous. In contrast to the control eye, it was found that the circulus iridis major and the anterior radial iridal arterioles as well as the two trunks of

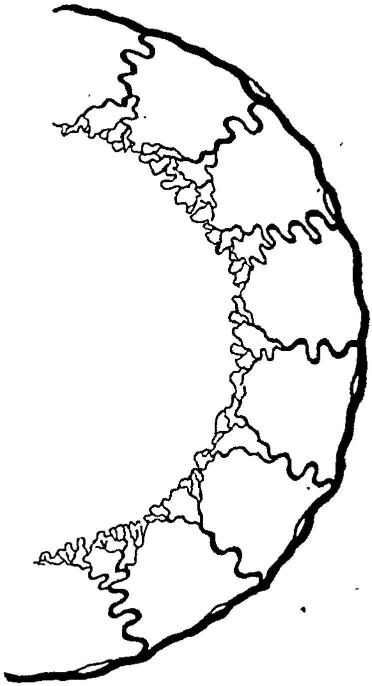

FIG. 1

FIG. 2.

FIG. 3.

FIG. 4.

Adrenaline: Partly schematic drawing of the vessels of the iris as seen with the slit-lamp (Fig. 1), and microphotographs of the iris after the benzidine reaction (Figs. 2–4). The dilatation of both the large vessels and the capillaries accompanied by the appearance of new vascular districts, especially in the pars pupillaris is characteristic.

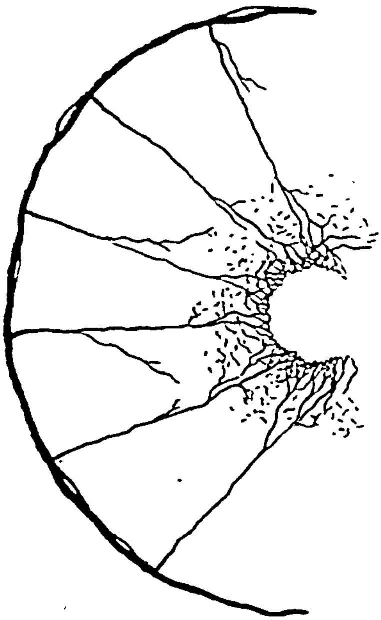

FIG 5.

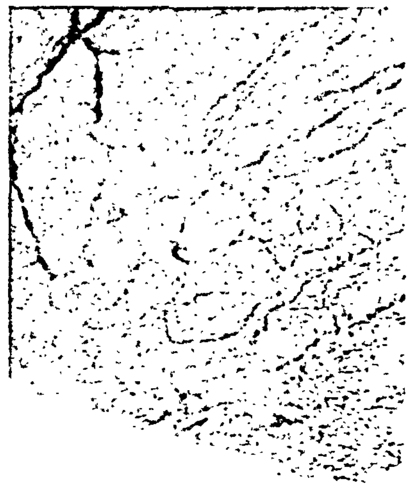

FIG. 6.

FIG. 7.

Pilocarpine: Partly schematic drawing of the vessels of the iris as seen with the slit-lamp (Fig. 5). and microphotographs of the iris after the benzidine reaction. Presence of numerous fine capillaries over the whole surface of the iris (Fig. 6), while the larger radial vessels appear normal in size and even reduced (Fig. 7).

the long posterior ciliary arteries which form the circulus iridis major in the rabbit did not appear dilated, whereas near the pupillary border these vessels divided in numerous small capillary arches. Moreover, towards the ciliary portion among the anterior radial arteries numerous small vessels were observed, forming a sort of capillary network.

Atropine (Fig. 11)

Here one is struck by an abnormal dilatation of the circulus iridis major and of the anterior arteries of the iris. I could not see any capillary network as in the preceding experiments. Near the pupillary region, however, I found some loop-formed arches, as are seen in normal eyes.

II

The eyes were subsequently enucleated from the surviving animals. The globes were cut parallel to the equator a few mm. behind the limbus. The lens and vitreous body were carefully removed. The iris as well as the retina and the choroid were detached from their bases in small rectangular fragments and examined with the dissection microscope. The microscopical findings were mostly analogous to those obtained biomicroscopically, so far as the anterior surface of the iris was concerned.

Adrenaline (Figs. 2-4)

The ciliary processes, in comparison with the control eye, appeared congested not only because of the dilatation of the arterioles but also because of an increase in their number. Near the pupillary border and throughout the whole surface of the iris I found tiny capillaries which did not occur in the control eye.

Pilocarpine and eserine (Figs. 6, 7, 9, 10).

The striking feature of the microscopical picture was the presence of numerous very fine capillaries uniting the single arteries, and the presence near the pupillary border of numerous capillary arches resembling a kind of *caput Medusae.* Inside the ciliary processes I found fewer vascular trunks than with adrenaline, at the most two or three, as occur in the normal eye. I cannot assert with certainty to have found any differences from the normal in the fragments of choroid examined. On the whole, the vascular dilatation here was less intense than after adrenaline and atropine.

Atropine (Figs. 12-13)

Microscopically the thin capillary network seen in the pupillary portion of the iris after the administration of pilocarpine and eserine was not seen, but there were scattered and irregular loop-formed capillary arches. In the choroid I observed a vascular dilatation which had been absent in the preceding cases.

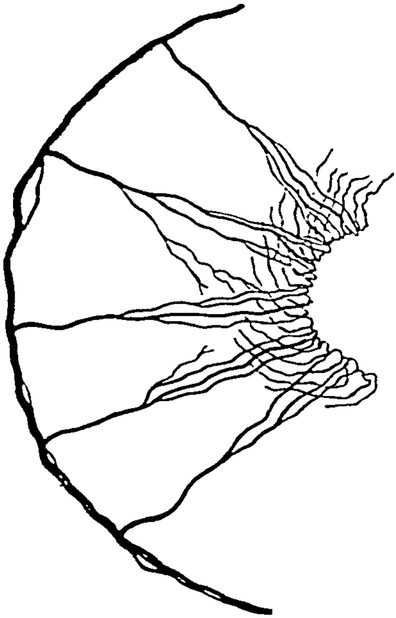

FIG. 8.

FIG. 9.

FIG. 10.

Eserine: Partly schematic drawing of the vessels of the iris as seen with the slit-lamp (Fig. 8), and microphotographs of the iris after the benzidine reaction (Figs 9 and 10). Appearance of numerous new capillary districts with dilatation of the smaller vessels, especially in relation to the pars pupillaris, without a corresponding dilatation of the large radial vessels of the iris.

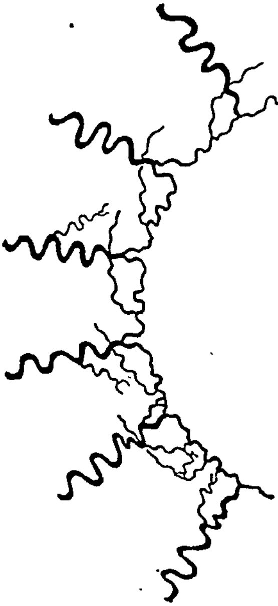

FIG. 11.

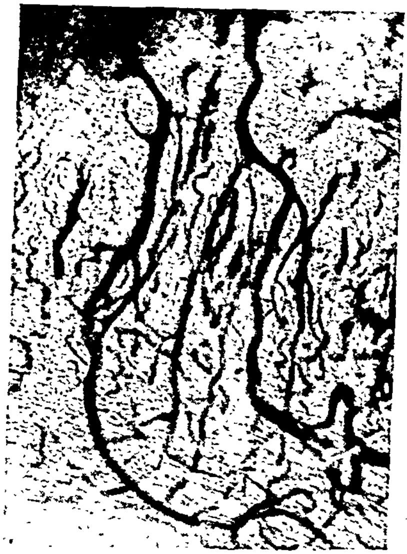

FIG. 12.

FIG. 13.

Atropine: Partly schematic drawing of the vessels of the iris as seen with the slit-lamp (Fig. 11), and microphotographs of the iris after the benzidine reaction (Figs. 12 and 13). Considerable vasodilatation and tortuosity of the large vessels of the iris without corresponding dilatation of the smaller vessels, and appearance of new capillary districts. The pars pupillaris does not show any tiny vessels (Fig. 13).

III

The fragments were subsequently fixed in a concentrated solution of common salt, sugar and formalin for three days, and finally the benzidine reaction (Pickworth's method) was performed.

From these biomicroscopic and microscopic findings, both in a fresh state and after the benzidine reaction, the following conclusions emerge which, incidentally, are in agreement with those of most investigators:

Adrenaline.—Arterial vasodilatation (probably also venous dilatation) and capillary vasodilatation followed by the appearance of new vascular districts.

Pilocarpine and eserine.—Capillary vasodilatation and opening of new capillary districts, without dilatation of the larger vessels.

Atropine.—Marked arterial vasodilatation (and probably also venous dilatation) without corresponding capillary vasodilatation and without appearance of new capillary districts.

DISCUSSION

The vasodilator effect obtained by the four drugs is clearly demonstrated by the preceding observations; but while atropine merely acts upon the larger vessels, adrenaline acts upon the capillaries as well, producing not only vasodilatation but also the appearance of new vascular districts. Pilocarpine and eserine exert their action on the capillary vessels with the opening of new vascular sections.

The difficulty in elucidating the effect of these drugs in primary glaucoma, especially with regard to their vascular action, derives from the fact that in this disease the conception of von Hippel and Gruenhagen is usually considered axiomatic. According to it a uveal vasodilatation is constantly followed by a rise in the intra-ocular pressure. As long ago as 1905 Angelucci questioned this physiological conception, which was based merely upon the experimental findings resulting from stimulation of the trigeminal nerve. Modern knowledge of general and ocular physiology has, however, raised doubts as to the validity of this conception.

Although the dialysis theory, *i.e.*, that the aqueous humour is a dialysate in thermodynamic equilibrium with the blood, does not now appear to explain all the facts (Duke-Elder and Davson), it is, however, indisputable that the height of the intra-ocular pressure must be regulated to a large extent by the hydrostatic pressure of the uveal capillaries and by colloid osmotic pressures. According to this conception, which has been generally accepted up to recent times, the intra-ocular pressure is established by the mean level of the capillary pressure less the colloid-osmotic pressure of the plasma proteins (Parsons; Henderson and Starling; Dieter; Duke-Elder; Magitot). The corollary to this

relationship is that a rise in the level of capillary pressure determines a rise in intra-ocular pressure when the colloid osmotic pressure of the plasma proteins remains unaltered.

General haemodynamic laws inform us that the hydrostatic pressure at any level of the vascular system is " proportional to the sum of resistances the liquid is forced to overcome " (Luciani). The conception of von Hippel and Gruenhagen, which we have already noted, may hold true, according to haemodynamic laws, only in the case of dilatation of the arteries, but not of the capillaries. Here, indeed, haemodynamics show that the sum of resistances increases instead of diminishing, as in the case of arterial dilatation, in spite of a considerable increase of the vascular bed. The corollary to this fundamental physiological fact is that two different variations in intra-ocular pressure occur according to whether there is an arterial or a capillary vasodilatation. In the former case, the sum of resistances encountered by the blood decreases, and therefore the mean capillary pressure increases, and this is followed by a rise in intra-ocular pressure; in the latter case, in spite of the considerable dilatation of the vascular bed, the sum of resistances increases and is followed by a fall in hydrostatic capillary pressure, and consequently in intra-ocular pressure.

The importance of these facts must be clearly remembered in any discussion on the regulation of the tension of the eye. The functional independence of the arterial circulation from the capillary circulation is certainly one of the most essential features in maintaining the intra-ocular pressure at a constant level, in spite of occasional sudden haemodynamic variations. In pathological conditions, as in primary chronic glaucoma, we must not forget that the rise of capillary pressure is one of the fundamental experimental findings (Dieter). Notwithstanding numerous experimental researches, no variation in blood composition or in the colloid osmotic pressure of the plasma proteins has been found in this disease.

The rise of the capillary pressure level in glaucoma, in haemodynamic terms, may be considered as a " *diminution of the sum of peripheral resistances encountered by the blood as far as the last capillary barrier.*"

From my previous experimental researches I concluded that one of the numerous causes of the rise in intra-ocular pressure in the glaucomatous eye is such a diminution of the sum of resistances. According to this hypothesis the cause is a reduction of the uveal capillary bed owing to the obliteration of numerous vascular districts. This hypothesis was based on the fact that in typical primary (simple) chronic glaucoma the choroid becomes thinner

and the capillaries are obliterated and disappear, as was particularly stressed by Elschnig. Further evidence is the fact that no rise in capillary pulse volume could be registered photoplethysmographically on the inspiration of amyl nitrite.

The effect of the action of pilocarpine and eserine, adrenaline and atropine, so characteristic in this disease, can be related with this essential aspect of the development and rise of intra-ocular pressure.

Pilocarpine (2 *per cent.*) *and eserine* (0·5 *per cent.*).

From a vascular point of view these drugs act by modifying the capillary circulatory " debit." As was already mentioned in the experimental part of this paper, their vasodilator action makes itself evident on the capillary vessels, even favouring the opening up of new vascular reserve sections. This was suggested by Krogh in 1924 at the Deutsche Ophthalmologische Gesellschaft, in view of the fact that the instillation of these drugs raises the albumen content of the aqueous humour, and has also been experimentally confirmed by Angelucci, Wessely, Dieter, and others. As has already been mentioned, the dilatation of the capillary bed will give rise to an increase in the sum of resistances and this increase cannot be compensated by a growth of the vascular bed. Consequently we shall note a fall in the level of the capillary pressure.

Indeed, by measuring the capillary pressure entoptically in glaucomatous patients Dieter found that this pressure falls after the instillation of miotic drugs. Again, Thomassen has recently observed in glaucomatous patients that the instillation of pilocarpine and eserine lowers the venous pressure in the episcleral vessels, whereas it is without any influence on the pressure in the episcleral arteries. Moreover, this author found experimentally that the lowering of intra-ocular pressure was secondary to the decrease in venous pressure.

Finally, the present hypothesis that pilocarpine and eserine increase the sum of resistances by dilating and opening new capillary districts may explain some experimental findings that have not yet found a solution. Gala, by means of sodium iodide, and Thiel, by means of fluorescein, found that in glaucomatous eyes after the instillation of miotic drugs the outflow of these substances into the aqueous is lessened, thus confirming Hess's entoptic findings as to the slowing of the blood flow.

In fact, following general physiological principles, the increase of the capillary bed brought about by pilocarpine and eserine will lower the capillary pressure as well as the rate of flow.

Atropine (1 *per cent.*).

My findings show that this drug produces vasodilatation in the larger vessels and has no influence whatever on the capillary bed. That its action on the capillaries is almost without effect is demonstrated by the fact that the instillation of this drug does not alter the concentration of albumen in the aqueous, as was found by Dieter and confirmed quite recently by Stocker. According to general haemodynamic laws, the arterial vasodilatation induced by this drug will determine a diminution of the sum of resistances in the glaucomatous eye. Dieter, indeed, found experimentally that the capillary pressure rises with the instillation of atropine. Since this occurs in a third of all glaucomatous patients, and when it does there develops at the same time an acute attack of raised tension, we may infer that in these cases the capillary bed, owing to its severe impairment, is no longer able to neutralize the diminution of the sum of resistances which follows the vasodilatation of the large arterial vessels. The consequence will be a rise in intra-ocular pressure and an infringement of the "law of circulatory rate," *i.e.*, the amount of blood passing through the the arterial section is not exactly equal to the amount passing during the same time through the venous section of the system. This would be comparable to the onset of certain pulmonary oedemas occurring in consequence of the altered ratio between the amount of blood passing through the pulmonary veins and the amount passing during the same time through the arterial pulmonary system.

Adrenaline (1 : 1000).

The vascular effects of adrenaline are to some extent similar to those already inferred for pilocarpine and eserine as well as for atropine. It is beyond doubt—and most investigators are of this opinion—that the greatest hypotensive effect obtained with this drug becomes evident during the period of maximal arterial and capillary vasodilatation. Like atropine, this drug actually dilates the large arterial vessels, thus diminishing the sum of resistances; but like pilocarpine and eserine it opens new vascular reserve sections, thus increasing the capillary surface. But the final result is an increase of the sum of resistances, owing to the growth of the capillary bed, thus bringing about a decrease of the mean capillary hydrostatic pressure.

This drug is probably contra-indicated in acute glaucoma because under certain experimental conditions, as was noticed by Poos, it produces an excessive permeability in the capillaries for the plasma proteins, and thus will determine a marked rise in intra-ocular pressure. In fact, as the balance of distribution is

almost equal inside and outside the vessels, an annulment of the osmotic membranes takes place, as if a river of fresh water enters into the sea. The level of the intra-ocular pressure would thus be determined only by the height of the vascular hydrostatic pressure, no longer antagonized by the colloid osmotic pressure of the plasma proteins, as in the equilibrium described by Henderson and Starling.

Finally, I wish to emphasize that the hypotheses so far put forward represent only an attempt to interpret the vascular action of these four drugs, and that further experimental investigation is required. As long as our knowledge of the origin and nature of the intra-ocular fluid is imperfect, however, it is impossible to offer a definite and complete explanation regarding the effects of these drugs, since the questions raised are intimately connected with the more essential problem of the development and rise of the intra-ocular pressure.

SUMMARY

1. Pilocarpine and eserine determine a vasodilatation and the opening of new capillary districts followed by an increase of the capillary bed without, however, dilating the large vessels. In the light of general haemodynamic knowledge this causes an increase of the sum of resistances in the circulation, in spite of a considerable growth of the circulatory bed. The fundamental corollary to this action is the fall of the mean capillary hydrostatic pressure and, therefore, of the ocular tension, as occurs in primary chronic glaucoma.

2. Atropine determines a dilatation of the large vessels without any corresponding capillary dilatation, and without opening up new vascular districts. According to haemodynamic laws, this brings about a diminution of the sum of resistances in the circulation, and therefore an increase of the mean capillary hydrostatic pressure, whenever the capillary bed, as in chronic glaucoma, is severely impaired and is no longer able to cope with such difficulties.

3. Adrenaline determines a dilatation both of the large vessels and of the smaller capillaries, followed by the opening of new vascular districts and by a growth of the circulatory bed. Like atropine, this drug dilates the large arterial vessels, thus diminishing the sum of resistances; but, like pilocarpine and eserine, it opens new vascular reserve sections, thus increasing the capillary surface. But the final resulting effect is the increase of the sum of resistances owing to the growth of the capillary bed, thus bringing about a decrease of the mean capillary hydrostatic pressure, and therefore of ocular tension.

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SLIT-LAMP EXAMINATION OF THE VITREOUS AND THE FUNDUS*

BY

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EXAMINATION of the vitreous body and of the fundus with the help of the slit-lamp enables us to understand better some pathological pictures, and often facilitates a differential diagnosis. Since more details are being revealed by this method, pathological changes can be detected early. Moreover, stereoscopic examination of the fundus is made possible by a cheap additional device to the slit-lamp which not only does the work of a binocular ophthalmoscope of Gullstrand, but gives better results.

* Lecture given May 8, 1948, to members of the British Faculty of Ophthalmologists at Berne.

The method consists in reducing as much as possible the angle between the illuminating arm and the microscope of the slit-lamp by means of a special prism (Fig. 1), and in eliminating the refraction of the cornea. We obtain this result with the help of a contact glass made of plastic. Instead of a contact glass, Lemoine and Valois, and later Hruby, used a concave lens of 55 dioptres in front of the eye. The contact glass affords a great field of vision, and in general cleaner pictures of the fundus when observed with a 20x magnification; it can be centred on the eyeball very easily. The astigmatic distortion in 20x magnification can be made very

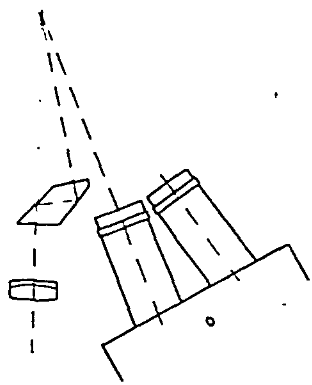

FIG. 1.

small, and even reduced to zero—especially if one examines with a short slit—when the point examined lies in a region about 25° round the posterior pole. By 10x magnification, this region is still greater. In certain cases—for instance shortly after intra-ocular operations—the concave lens is preferable.

In such an examination, the most important point is to see the vitreous and the fundus *stereoscopically*. This is the chief condition for seeing fine details and avoiding deceptive pictures. After having dilated the pupil to a maximum, one always succeeds in seeing a great part of the fundus stereoscopically. The apparent place of the object observed with our model of the slit-lamp (Haag-Streit) being in the axis of revolution of the whole instrument, the picture does not move if the microscope and illuminating arm are turned about this axis. Thus one always finds a position where the observed point of the fundus is seen stereoscopically. Lateral movements of the instrument make other points of the fundus appear in the field of the microscope.

For examination of the vitreous the angle between the illuminating arm and the microscope is made as wide as possible if one

wishes to eliminate the reflected light from the fundus during the examination in focal light.

On the contrary, if one intends to examine fine changes of the vitreous in reflected light by the slit-lamp, the red reflex of the fundus affords the luminous background. For this purpose and for the examination of the deeper parts of the vitreous, the angle of the slit-lamp must be reduced. The most important change in the vitreous, besides inflammatory disorders and bleeding, is its detachment: one sees the vitreous framework condensed in the inferior part of the vitreous space and limited upwards by a border against an optically empty space (Fig. 2). The framework of the vitreous extends upwards only behind the lens. In front of the papilla, there is a more refractive glassy ring or thread upon the posterior border of the vitreous. In some cases, the point where the vitreous still adheres to the retina is easily visible.

In many cases of detachment of the retina one can see exactly where the *corpus vitreum* pulls on the borders of the hole. On the whole, biomicroscopy often shows clearly the mechanism of the origin of a detachment of the retina. This can be illustrated by a case.

We first saw the patient in February, 1945, in our clinic. He had had repeated haemorrhages into the vitreous. He had now a detachment of the vitreous in the upper part, but downwards an early flat detachment of the retina. In the upper part one saw here and there blood elements in front of the retina, and in the lower part, in the region of the detached retina, an extended horizontal blood-line; just above this blood-line (Fig. 3) was a triangular hole in the retina. With the slit-lamp, one saw that this curious blood-line showed how far the vitreous was detached from the retina. Underneath this line, retina and vitreous were connected together, and above this line they were separated. Blood had collected in the pocket between vitreous and retina, forming a transverse streak. The detachment of the vitreous extended only as far as the lower border of the hole in the retina. From there began a combined detachment of retina and vitreous. The mechanism of the repeated haemorrhages and of the hole in the retina was the following: As usual, the detachment of the vitreous had begun in the upper part. Owing to vascular lesions of the retina, there occurred haemorrhages as seen sometimes in elderly people. We know that a detachment of the retina often begins with haemorrhages into the vitreous. Now the detachment of the vitreous progressed, causing from time to time small haemorrhages, and finally a tear in the lower part of the retina where the detachment of the vitreous body had largely progressed. From that time, no further detachment of the vitreous followed, but vitreous and retina together detached themselves from the choroid and remained connected with each other. The genesis of this process was proved by the further history of the case. The hole was coagulated by diathermy and the patient was kept in bed in a half-sitting position, as Gonin recommended for holes in the lower region of the eye. The retina did not attach itself. We supposed that the cause of the failure was that in a sitting position the vitreous pulled down the retina from the choroid. Therefore, after a second intervention, the patient was kept flat on his back so that the vitreous pressed the retina towards the posterior wall of the eyeball, and the detachment was cured.

In eyes with inflammatory changes in their posterior part, either uveitis or neuritis, one often notices a Tyndall phenomenon* in

* Aqueous and other forms of flare are known in Switzerland as the Tyndall phenomenon.

FIG. 2

Hans R. aged 28 years. R. eye. State after juvenile haemmorrhage into the vitreous detachment of the vitreous. Illumination from the left side. 10×.

FIG. 3

Fritz S. aged 55 years. R. eye. M : site of the macula. P · site of the papilla. V: back border of the detached vitreous. R: detached retina. Ch : Choroid. H : triangular hole in the retina. B : pre-retinal haemorrhage in the pocket between detached vitreous and retina Illumination from left. 20×.

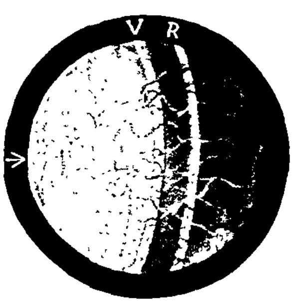

FIG. 4

Fritz A. aged 55 years. R. eye. Retinitis proliferans diabetica. Vascularisation of the back vitreous membrane. V : Section of the back membrane of the vitreous. R: Section of the retina. The vessels of the membrane are visible directly on its section and in the light reflected by the fundus. 20×.

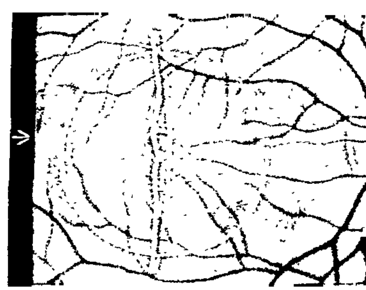

FIG. 5

Jakob B. aged 35 years. R. eye. Chorio-retinitis centralis serosa. Illumination from the left side. 20×.

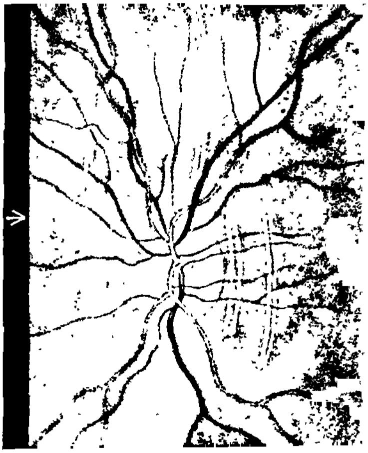

FIG. 11

Rosa I. aged 35 years. L. eye. Choroiditis disseminata. In the upper part fresh inflammation; beside the papilla old foci.

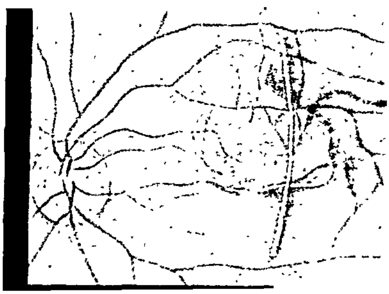

FIG. 12

Erika M. aged 68 years. L. eye. Old focus of choroiditis centralis with depressed choroid and thinned retina.

the posterior vitreous space. In cases of periphlebitis retinae, the posterior limiting membrane of the vitreous is detached from the retina and the vessels of the proliferating scars are situated in this membrane (Bangerter-Blaser, Hruby) (Fig. 4). At the onset of many retinal diseases (for instance chorioretinitis), the posterior limiting membrane of the vitreous is detached from the retina and visible in the optical section as a very fine greyish line. In the reflected light of the fundus, in such cases, one often sees in it fine precipitates.

Slit-lamp examination of the fundus is the best method for examining the posterior part of the retina, especially the macula. If one examines the retina in the large pencil of the slit-lamp the slightest traces of irregularities in thickness appear as irregularities of the surface reflexes.

By observing a normal retina with the slit-lamp, one sees very clearly the configuration of the papilla, the nerve fibres of the retina, the depression of the fovea, and the thickness of the retina in the cross-section. The thickest part of the normal retina is situated on the temporal side of the papilla and around the macula, where one sees, by ophthalmoscopic examination, the wall-reflex of the macula. The normal retina is thinnest at the fovea.

Slit-lamp examination has its greatest value in the following changes:

1. Papilloedema, which can be seen as well by this method as with the binocular ophthalmoscope of Gullstrand. We cannot agree that slit-lamp examination shows definite differences between early papilloedema and papillitis. We have seen detachment of the limiting membrane in both. Certainly the flattening of the central depression of the papilla does not constitute a differential sign between neuritis optica and papilloedema, nor could we see with a 20x magnification perivascular lymph spaces. However, in cases of true papillitis we often see a distinct Tyndall phenomenon in front of the papilla, or fine precipitates on the detached vitreous membrane.

2. Retinitis centralis serosa gives a very characteristic picture. If this disease is situated just in the macula including the fovea, the perifoveal part is prominent, with an umbilical depression in the fovea, so that the optical section of the retinal surface resembles a Cupid's bow (Fig. 5). The retina is not disturbed. Its posterior limit is not distinct. In front of the choroid there seems to be an empty interval. White spots are visible in front of the choroid, apparently situated on the invisible posterior border of the retina. In front of the oedematous retina, we saw, in our latest cases, a very fine vitreous membrane, a sign of a slight detachment of the vitreous. At first the aspect of the choroid is almost unchanged.

Later on, it becomes slightly marbled. This disease is often mistaken for retrobulbar neuritis, for it is accompanied by a relative central scotoma, generally with only little decrease of visual acuity. Subjectively, there is a yellowish positive scotoma, best visible just after awaking; metamorphopsia exists, easily demonstrable by means of the Amsler lattice. During the disease, the refraction is more hypermetropic than before or after. All these characteristic signs are less pronounced if the changes are situated away from the fovea (Fig. 6). Then the complaints of the patient are indistinct: slightly blurred vision, and a certain distortion of lines. In such cases, the correct diagnosis is seldom made without an examination with the slit-lamp. One mostly assumes nervous disorder, especially because chorioretinitis centralis serosa is often found in vasolabile individuals. The aetiology of this affection is not known, but vasolability seems to favour it. As therapy, we use with success a series of intravenous injections of mercury cyanide (daily 1 c.cm. 1 per cent. solution, 20x) with the usual control of urine and mouth. This disease is not rare, but often overlooked.

3. With the help of biomicroscopy of the fundus, it is very easy to discern little spots of capillarosis from Drusen of the choroid. Capillarosis spots (as signs of a vascular disturbance of the retina) are situated within the thickness of the retina and are always opaque and white; with the slit-lamp often one sees their shadows on the screen of the choroid (Fig. 7). Drusen are situated on the surface of the choroid; their colour is generally yellowish (Fig. 8). When illuminating their neighbourhood, one often sees a golden reflex on their borders. But there exist also little white inclusions on the surface of the choroid not protruding from it. The ophthalmoscopic picture they present is like that of capillarosis spots. Only by the slit-lamp is differentiation possible.

4. Oedema of the retina can be seen very easily. Cystic oedema of the macular region has an extremely beautiful aspect (Fig. 9). The differential diagnosis between cysts of the macula and holes in the macula—which is very difficult with other methods—is very simple by means of biomicroscopy.

A cyst of the macula has an anterior wall which does not appear in the case of a hole (Fig. 10). Little cysts are often more easily visible by indirect illumination than in the focal light of the slit-pencil. Cystoid oedema of the macula is frequent in cases of uveitis, vascular disturbances of the posterior pole of the retina and the choroid (for instance thrombosis of the central vein, arteriosclerotic changes of the choroidal vessels at the macula); in degeneratio disciformis maculae (Junius-Kuhnt); in older detachments of the retina, also sometimes in re-attached cases. However, there are rare cases of cystoid oedema without an assignable cause.

In cases of malignant hypertension, one frequently finds considerable oedema of the retina (without cysts), together with capillarosis spots, haemorrhages and "cotton-wool" degenerations of the nerve fibres. This oedema is very turbid, so that the choroid is seen only indistinctly. On the other hand, in many cases of pure diabetic retinopathy and in Junius-Kuhnt disciform degeneration, a glass-like thickening of the retina appears, so transparent that the shadows of the retinal vessels are seen clearly on the surface of the choroid. The layer where a haemorrhage is situated can be determined exactly.

5. The normal surface of the choroid is smooth. With some aged people it looks rough, as if treated with emery paper. In certain cases it gives the impression that this picture preceded a Junius-Kuhnt disciform degeneration.

6. The differential diagnosis between a detachment of the retina and a tumour of the choroid may be difficult. But if one sees, with the slit-lamp, the bulging tumour behind the detached retina, the diagnosis is much easier.

In a case of angioma of the choroid beside the papilla—the diagnosis was made *after* enucleation—the retina in front of the tumour was very thickened and there was an extensive cystic degeneration. In view of the fact that in histological preparations of this disease an extensive cystic degeneration of the retina is almost always found in front of the tumour, the presence of an extensive cystoid degeneration in front of a tumour not at the macula may be of diagnostic value.

7. It seems to be of practical importance that in cases of choroiditis the retina is blurred and often slightly thickened in front of a focus of fresh inflammation (Fig. 11). Healed choroiditic scars are usually a little depressed, and the retina in front of them is of glass-like transparency. In old disseminated choroiditis (Fig. 12) it is sometimes very difficult to determine by means of the ophthalmoscope if there is fresh inflammation on the border of an old focus; slit-lamp examination enabled us to do so.

This short survey may show the diagnostic importance of slit-lamp microscopy of the fundus.

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BLOOD-VESSEL FORMATION IN THE CORNEA*

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UNIVERSITY OF GLASGOW

INTRODUCTION

THE experimental production of corneal vascularisation has been performed by various workers. Ehlers (1927) made daily applications of ethyl alcohol to rabbits' corneae resulting in a loss of corneal transparency and an ingrowth of vessels from all round the limbus into the anterior two-thirds of the cornea. Julianelle (1933) produced "pannus" formation by intra-corneal injection of proteins after sensitisation of rabbits and monkeys. Mann (1943) described new-vessel formation in the cornea after application of mustard gas and related substances. In none of these methods was the injury sufficiently localised or of an intensity constant enough for our purpose.

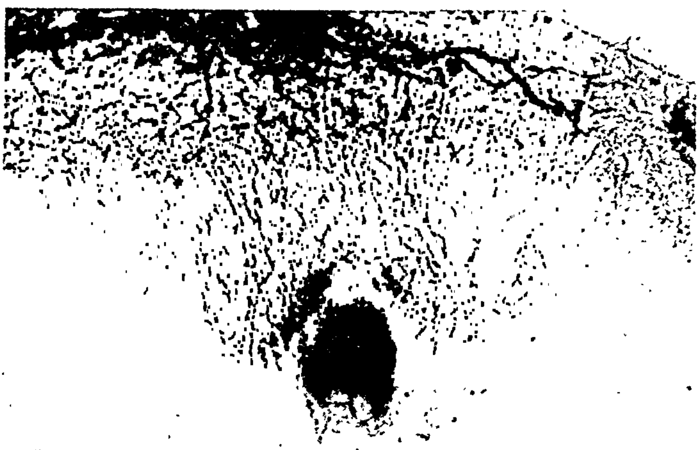

FIG. 1.

Note the isosceles triangular area of vascular infiltration from the limbal plexus above.

From clinical observation it is known that, if a localised lesion of the cornea is accompanied by vascularisation, the vessel formation usually begins at the part of the limbus nearest to the lesion, and that it often tends to take a triangular form as indicated in Fig. 1. We decided to study this phenomenon in rabbits under

* Received for publication, August 11, 1948

standard conditions unattainable in clinical work, and this series of experiments was designed to discover if the site of a localised injury such as a burn had any effect on the formation of these new vessels from the limbus.

METHOD

A " standard lesion " was produced by applying a platinum wire cautery to a rabbit's cornea for approximately two seconds. The cautery was kept at a uniform temperature throughout the experiment by supplying a constant voltage. Two minutes before cauterisation two drops of 1 per cent. pontocain hydrochloride

FIG. 2.

The lesion involves the epithelium and the anterior two-thirds of the stroma.

were placed in the conjunctival sac. The burn to each cornea was repeated daily on the same site for the duration of the experiment, usually 10-14 days. The lesion was about 1 mm. in diameter and involved the epithelium and the superficial two-thirds of the substantia propria (Fig. 2). With two exceptions infection of the wound did not occur. The distance of the injury from the limbus varied from rabbit to rabbit, although the injuries were placed along the same meridian—usually 12 o'clock.

At the end of the serial cauterisation the rabbit was anaesthetised with ether, a carotid artery exposed, and a cannula inserted directed cranially. Five to ten c.c. of a 50 per cent. dilution of Indian ink (Reeves) in water was then run in under a pressure of 100 to 150 mm. Hg until the vascularised area of the cornea was filled

with ink particles. The animal was killed, the eye excised and placed in 10 per cent. neutral formalin. For examination the whole corneal thickness, including the limbus, was mounted in glycerine. The vascularised area was measured with a microscope eyepiece-micrometer and with a Vernier moving stage.

RESULTS

Experiment 1. The right corneae of five young adult rabbits were cauterised daily for 13 days. In four of the corneae a typical triangular vascular area was produced. The results are presented in Table I. In these corneae, as in the others subsequently examined, the vascular triangle was isosceles (Fig. 1).

TABLE I

Rabbit	Distance of lesion from limbus in mm.	Size of isosceles sides in mm.
A	1·7	3·3
B	1·7	3·3
C	2·1	3·2
D	2·1	3·2
E	4·2	No vascularisation

In rabbits A and B with a lesion 1·7 mm. from the limbus, the length of " d " (Fig. 3) was the same—3·3 mm. That is, vessels grew from all parts of the limbus within 3·3 mm. of the centre of the lesion. Again, in rabbits C and D, with a lesion 2·1 mm.

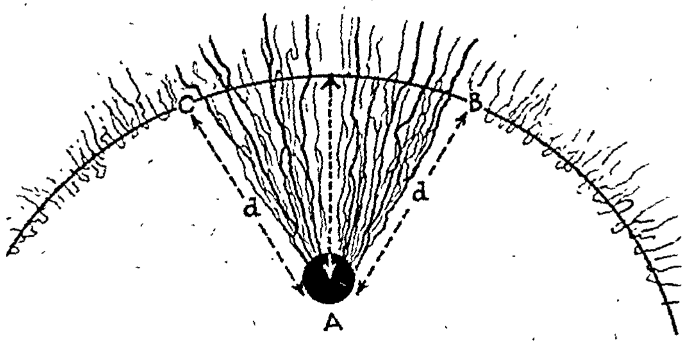

FIG. 3.

A diagramatic representation of the vascular triangle. The vessels do not all grow towards the lesion as shown, but tend to grow towards the centre of the cornea (Fig. 1).

from the limbus, vessels grew from all parts of the limbus within 3·1 mm. of the lesion. On the other hand, when the lesion was placed 4·2 mm. from the limbus as in rabbit E, the limbal vessels were not affected, and no vascularisation was produced.

The approximation of the measurements for " d " in these four corneae (3·3, 3·3, 3·1 and 3·1 mm.) stimulated us to repeat the experiment on a larger scale in order to investigate further the degree of constancy of " d " for a standard lesion.

Experiment 2. This experiment was carried out along similar lines, but both corneae were injured in each rabbit. In this group, only 10 successive daily cauterisations were done. Moreover the cautery point was larger and the temperature was slightly higher. The standard lesion, although constant within this group, was therefore different from that used in experiment 1.

The results in the second series of 8 rabbits involving 16 corneae are shown in Table II. Triangular areas of corneal vascularisation were obtained in all the eyes. The experiment on the left eye of rabbit G was spoiled by an error in the technique. In rabbit F the wounds became infected, as shown by general redness of the conjunctiva and a discharge from the eyes. All the other eyes were white and without discharge. We therefore excluded the results from these animals.

TABLE II

Rabbit	Eye	Distance of lesion from limbus in mm.	Size of isosceles sides " d " in mm.
A	Rt.	1·4	4·0
E	Lt.	1·9	4·4
C	Lt.	2·1	4·3
D	Lt.	2·1	4·4
H	Lt.	2·1	3·9
B	Rt.	2·2	4·4
D	Rt.	2·2	4·4
E	Rt.	2·2	4·2
A	Lt.	2·3	4·3
H	Rt.	2.4	3·8
G	Rt.	2·5	3·9
C	Rt.	2·7	4·2
B	Lt.	3·3	4·3

In the remaining 13 corneae the distance from the centre of the " standard lesion " to the basal angle of the vascular triangle is fairly constant. The mean of the measurement of " d " in these 13 corneae is 4·2 mm. with a standard deviation of 0·21 mm. The range is from 3·8 mm. to 4·4 mm.

In corneae H rt. and H lt. a triangle of pigment was noted to occupy the same position as the vascular area (Fig. 4). In the remaining rabbits limbal pigmentation was very slight or absent.

FIG. 4.

Note the migration of pigment from the limbal pigment ring below.

Experiment 3. Six rabbit corneae were injured under conditions identical with experiment 2. The "standard lesions" were made at 4·5, 4·6, 4·8, 5·0, 5·1, 5·3 mm. from the limbus. In no case was ingrowth of limbal vessels observed.

DISCUSSION

A localised lesion, in the rabbit's cornea, placed within a certain distance from the limbus, can produce an area of vascularisation which has the form of an isosceles triangle. If, however, the lesion is placed beyond this distance no vascularisation is observed. Further, there is a relatively constant distance between the site of the lesion and the basal angles of the vascular triangle (the distance "d" Fig. 3). These findings could be accounted for by assuming that a factor, which is produced by the corneal lesion at A (Fig. 3), diffuses from that situation equally in all directions, and in doing so becomes less effective the further away it is from A. The amount of this factor present at the angles B and C at the base of the vascular triangle would represent the minimum amount of the factor capable of stimulating limbal vessels to bud. Beyond B and C the concentration of the factor is apparently too low to stimulate budding.

The shape of the resulting vascular area can be readily appreciated by studying Fig. 5. Each large black circle represents a standard lesion, and the distance between the concentric lines is 1 mm. A factor diffusing from the lesion will become weaker,

the further it is from the source. Let us assume that, for this particular lesion, the factor is able to stimulate vascularisation up to the 3 mm. ring, while beyond this distance the factor is too weak to produce new vessels. It can be seen from Fig. 5 that, although the shape of the vascular triangle varies according to the distance of the lesion from the limbus, the distance from the lesion to the basal angles of the triangular area remains unchanged.

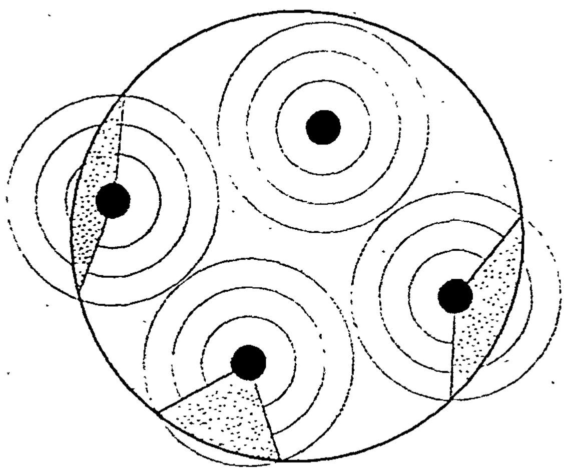

FIG. 5.

The black circle represents the standard lesion. The concentric lines are placed at 1mm. intervals. The shaded area indicates the theoretical shape of the area of infiltration.

The distance "d" (Fig. 3) is the radius of the zone in which the concentration of the "factor" is sufficient to produce vascularisation from the limbus.

The findings would then appear to offer evidence that new-vessel formation in the cornea, in the circumstances described, depends on a factor released by the primary lesion and diffusing from the site of the lesion.

Studies of the retina have also shown evidence of the presence in that tissue, in certain circumstances, of a factor or factors able to influence the budding of new vessels (Michaelson, 1948).

The nature of the factor liberated at the site of the burn might possibly be a substance similar to histamine directly affecting the limbal vessels. On the other hand there is evidence accumulating which suggests that there may be present in the normal corneae a

substance, or substances, which prevent the invasion of limbal vessels (Wise, 1943; Bacsich and Riddell, 1945; Bacsich and Wyburn, 1947). Destruction of this substance around the site of a thermal burn would allow new-vessel invasion of the cornea in a manner similar to our findings.

According to Mann (1944), pigmentation of corneal epithelium is evidence of healing by "sliding" of epithelial cells from the limbus on to the cornea. In the two corneae in our second series where pigmentation was present, the pigment was distributed in

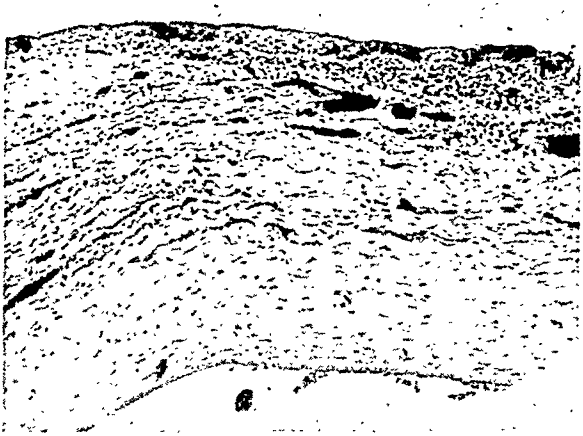

FIG. 6.

The epithelium is above. The vessels occupy the anterior two-thirds of the cornea. There is also considerable cellular infiltration.

a triangular form and co-extensive with the underlying new vessel formation. Furthermore, the vessels occupy the anterior half of the substantia propria and epithelium (Fig. 6). To us this raises the possibility that there may be a common mechanism influencing epithelial sliding and new-vessel formation.

This work has raised a number of interesting problems about the nature of the new-vessel stimulus, and it is hoped that further investigation will provide a clue to its structure.

SUMMARY

(1) A method is described for producing a relatively standard corneal lesion in rabbits and for studying the resulting vascularisation of the cornea.

(2) If the lesion is greater than a certain critical distance from the limbus no vascular response occurs. At less than this distance

from the limbus, vascularisation occurs, and the vascular area has the form of an isosceles triangle.

(3) If a series of "standard lesions" be placed at different distances from the limbus, but within the critical distance for that lesion, the distances between the sites of the lesions and the basal angles of the triangular vascular areas are fairly constant.

(4) The results suggest that the new-vessel formation in the cornea, in the circumstances described, involves a factor released by the lesion and diffusing from the site of that lesion.

We are indebted to Prof. R. C. Garry for helpful criticism and encouragement.

The cost of this investigation was defrayed by the Rankin Medical Research Fund.

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BOOK NOTICES

Principles and Practice of Ophthalmic Surgery. By E. B. SPAETH. Fourth edition. Pp. 1044. 8 colour plates, 649 figs. References in text. Henry Kimpton, London. 1948. Price, £3 15s. 0d.

This edition follows the lines of its predecessors, and like them will be warmly welcomed. In the writing of text-books on ophthalmic surgery, it is difficult to find the mean between, on the one hand, the author's personal practice, which is often so individualistic as to be of little value except to himself and those who are psychologically in relation to him, and, on the other, a compilation of the views of the many distinguished exponents of ophthalmic surgery as an art, a compilation which would be so compendious as to be useless and to appal even the stoutest-hearted bibliophile. The work under review has long been recognised to be as happy a compromise as may perhaps be expected in an imperfect part of the world where scientific doctrine and practice are as yet independent of the state, although, even in it, some may have considered that an undue amount of space has been devoted to the principles of plastic surgery and reconstruction; this criticism, however, is hardly valid in the aftermath of the war.

In the present volume the section on traumatic conditions has been amplified, and further material has been added in the sections dealing with paralytic squint and ptosis. Additions have also been made in the sections on exophthalmos and plastic surgery of the lids, while the section on enucleation has been rewritten to cover the recent work on plastic implants. Other minor additions have been made and the book has generally been brought up-to-date.

Refraction of the Eye. By A. COWAN. Third edition. Pp. 287. 187 figs. Bibliography. Henry Kimpton. London. 1948. Price, 27/6.

This book, in the opinion of the reviewer, is of considerably less value than many others which have been written on the subject. It follows the usual scheme of works of this nature; the first section deals with the physical optics of reflection and refraction, and while the mathematical exposition of the principles involved may be perfectly clear to those already familiar with the subject, one feels that the student preparing for an examination would be left somewhat bewildered, since the exposition hardly starts from first principles.

The succeeding chapters consider the eye as an optical instrument, and its ecological efficiency as such. A chapter on ametropia follows and one is, in the light of recent work, surprised to read that in myopia, in the absence of disease, it is safe to assume that the eye is anatomically too long. Nor will everyone agree with the author's views as to the importance of low-grade inflammation in the genesis of pathological myopia.

In discussing methods for the determination of refraction once again one feels that, as a practical guide, the chapter is of little value since, although much information is given, this is mainly suited to those who already have a considerable grasp of the theory and practice of the subject. The same criticism might perhaps apply to the succeeding section on the management and treatment of ametropia. The last chapter of the book gives a very elementary and short outline of the value of contact and telescopic lenses.

Altogether we feel that the book falls between two stools; its approach is not sufficiently elementary for the tyro, while, for the established refractionist, although it contains contentious passages which are always stimulating, it will do little to divert him from his established practice, however many heresies that practice may contain.

An Introduction to Clinical Orbitonometry. By A. C. COPPER. Pp. 125. 14 figs., 24 graphs. Stenfert Kroese (Leiden). Henry Kimpton, London. 1948.

The importance of estimating the resistance encountered in forcing the globe backwards into the orbit in the diagnosis of

orbital tumours was stressed by v. Graefe, but for over half-a-century such estimations depended on digital palpation alone. Langenhan was the first to devise an instrumental method of recording the orbital resistance (or tension); since his time three others have been suggested, but the orbitonometer devised by Copper has considerable advantages over them all. It consists of a dynamometer fixed to a supporting bridge which rests on the outer margins of the orbit and can be made to press the globe backwards by means of a plastic contact lens resting on the cornea and sclera. Readings of the displacement of the eye are then taken at intervals under increasing weights up to 400 gms. The instrument is suitable for general clinical use and is compact and easy to apply.

With this technique Copper has studied the retrobulbar resistance in 60 normal persons and has obtained a series of normal orbitonometry curves, their shape depending essentially on the volume of the retrobulbar space and the "orbital tension" which itself is composed of such factors as the tone of the extrinsic muscles, the amount of fluid which can be expressed from the orbit, and the consistency of the tissues. He has extended this study to pathological cases, particularly Graves' disease, exophthalmic ophthalmoplegia, acromegaly, intra-orbital inflammations, tumours and pseudotumours. In each of these diseases modifications of the normal curves are obtained. The resistance of the oedematous orbit of thyrotoxicosis can be differentiated from that of the infiltrated orbit of the exophthalmos not associated with hyperthyroidism, and space-taking lesions can be diagnosed before proptosis has developed. There is no doubt that, although the method cannot provide the differential diagnosis of a lesion such as a tumour, it is of great value in proving the presence of an abnormal density in the retrobulbar tissues, and providing objective information as to whether the process is progressive or stationary: the new instrument designed by Copper and the work he has done on its standardisation are advances in ophthalmological technique of considerable value.

Practical Orthoptics in the Treatment of Squint. By T. KEITH LYLE and SYLVIA JACKSON. Pp. xii and 251. 151 figs. Third edition. H. K. Lewis, London. 1949. Price 35/-.

Routine orthoptic supervision of children in Great Britain was curtailed from 1939 to 1946 by reason of transport difficulties, together with the absence of many orthoptists on war service. Nevertheless solid progress has been achieved during those years. Cases of ocular muscle imbalance occurring in the armed forces have been investigated and treated by new methods, many of which are applicable to children, although they could not readily have been evolved without preliminary trial among adult patients. Miss Billinghurst and Miss Salsbury appear to have made good use of

their Service experience, and each has been teaching and practising orthoptics for a number of years. Therefore Mr. Lyle is to be congratulated on having chosen worthy successors of Miss Jackson, the latter having now retired.

The format of this new edition, with its increased width of page, allows more scope for the larger illustrations, especially the Hess charts, and much important new material has been added. We predict a warm welcome for this amply-illustrated volume, which has been well printed on high-quality paper, and enclosed within dignified covers. A new edition of Practical Orthoptics was badly needed, not only because of the fresh methods of binocular stimulation devised since 1940, but also for the sake of stressing *differential* prognosis. Thus we read on pp. 34-35: "On no account should treatment be continued unless progress is being made . . . . time should not be wasted giving orthoptic treatment to patients whose binocular anomalies are unlikely to benefit from such treatment. Every orthoptist should clearly understand the limitations of orthoptic treatment as well as its advantages."

Realism is the keynote of the work under review. The importance of preliminary investigation and accuracy of diagnosis are duly emphasised. The serious reader will soon notice that Mr. Lyle avoids facile generalisations, and is careful to illustrate his principles by actual case-records. Torticollis—a subject which has often been clouded by obscure descriptions in the past—is lucidly expounded, and the account of cases exhibiting abnormal head posture will repay detailed study. Mr. Lyle's wide experience in the refractive, orthoptic and operative treatment of squint and other anomalies of ocular muscle balance is backed by his constant awareness of the human problem. That is why he insists upon the need for encouragement and cheerfulness on the part of the orthoptist, with the object of strengthening the patient's will to be cured. Another great asset is Mr. Lyle's special knowledge of neuro-ophthalmology, which is evident on nearly every page. Practical Orthoptics is a distinguished piece of work, the influence of which will be enormous throughout and beyond the English-speaking world.

CORRESPONDENCE

GLIOMA OF THE RETINA

To the Editorial Committee of

THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—I should be glad of the help that some of your readers may be able to give on this issue: To what extent is an

individual successfully treated for glioma of the retina liable to pass the affection on to his children?

That there is a hereditary factor in glioma of the retina is fully established. What is not known is whether all gliomata are hereditary. This could only be established if adequate information were available on the progeny of individuals successfully treated. There must be by now many patients who have reached adult life having lost one or both eyes in infancy (or retained an eye after successful radiotherapy). Some of these adults may have families, and it would be a great help to know whether any of their children have developed glioma. For a clear answer it is, of course, necessary to have information on children who are not affected as well as on children who are affected. If, as is assumed, glioma of the retina is dominant, 50 per cent. of the children of surviving patients should be affected unless modifying factors disturb the ratio.

In most dominant conditions tracing the family backward gives enough information. In the case of a highly lethal affection like glioma of the retina this procedure is not available. Moreover, there is good reason for believing that most cases of glioma represent new mutations rather than the continuance of a line of affected individuals.

I should be grateful if such of your readers who have the relevant information could let me have the following particulars:

(*a*) Name and a short personal history of the individual affected with glioma, and an indication, if available, as to the occurrence of glioma in relatives.

(*b*) The number (and, if possible, the sequence) of children in the second generation.

(*c*) Indication as to which, if any, of these children show glioma.

(*d*) In any glioma patients information as to whether the glioma was unilateral or bilateral would be appreciated.

Yours faithfully,

ARNOLD SORSBY.

ROYAL COLLEGE OF SURGEONS
LINCOLN'S INN FIELDS,
LONDON, W.C.2.
January 15, 1949.

To the Editorial Committee of

THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—The infection of the conjunctival sac by larvae of flies (maggots) is relatively rare in Western Europe (Duke-Elder, Vol. II), and most of the cases recorded have been infections by the *hypoderma bovis*.

Whilst in Malta I obtained larvae specimens of *oestrus ovis* and submit the following case history:—

During July a Naval officer attended the Ophthalmic Department of the Royal Naval Hospital, Malta, complaining that following a swim in the sea the previous day something had entered his right eye, producing redness and irritation. Examination revealed three small worms crawling on the conjunctiva, each approximately 1·5 mm. long.

These were removed with forceps and the eye irrigated. In 48 hours the patient had recovered from the traumatic conjunctivitis.

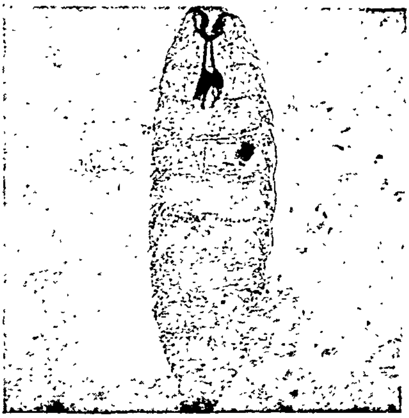

FIG. 1.

FIG. 2.

(During that period he used protargol drops 3 per cent.). No further attendances were necessary.

The specimens of the "worms" were mounted and have now been identified as larvae of *oestrus ovis*.

I am submitting two photographs of the larvae in case they should be of interest.

Yours faithfully,

GEORGE E. ROBINSON.

Surg. Lt.-Cdr. R.N.V.R.
Late Ophthalmic Specialist,
Royal Naval Hospital, Malta.

ROYAL INFIRMARY,
SHEFFIELD, 6.
December 2, 1948.

The ROYAL INSTITUTE of PUBLIC HEALTH & HYGIENE

Spring Session, 1949—Lectures to be delivered in

THE LECTURE HALL, 28, PORTLAND PLACE, W.1.

April 20 ... (1) "Occupational Eye Diseases and Injuries" *(Illustrated)*
April 27 ... (2) "Occupational Eye Diseases and Injuries" *(Illustrated)*

At 3.30 p.m. on each day.

Lecturer: Joseph Minton, F.R.C.S.

Chairman: Charles B. Goulden, O.B.E., M.A., M.C., M.D., F.R.C.S.

The next meeting of the Oxford Ophthalmological Congress will be held on July 7, 8 and 9, 1949, at Oxford.

THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

MAY, 1949

COMMUNICATIONS

PATHOGENESIS OF CONCURRENT EYE AND JOINT DISEASES*

BY

ERIK GODTFREDSEN

COPENHAGEN

THE reasons for discussing the subject of concurrent eye and joint diseases in this Society are (*a*) the great interest displayed in it by Swedish clinicians (Sjögren, Stenstam, Stig Holm, Edström and Osterlind); and (*b*) the recent advances concerning the physio-pathology and serological diagnoses of the joint diseases (blood cultivation and antibody measurements, including the antistreptolysin titre and agglutination test). These advances, together with the intensified research work within the field of allergy, which has led to the discovery of the antihistamine substances, as well as to the unfolding of further possibilities in virus pathology (thanks to the electron microscope and better methods of cultivation) have thrown new light on various joint diseases. As the aetiology and

* Read before the Swedish Society of Ophthalmologists at its Annual Meeting, June 5, 1948, in Gothenburg.

pathogenesis of many cases of iridocyclitis, scleritis and phlyctenular conjunctivitis are still obscure, and as these diseases are very frequently met with in association with joint diseases, it might be of interest to analyse the nature and frequency of eye symptoms in joint diseases in order thus to attempt to elucidate the pathogenic conditions.

The clinical pictures of concurrent eye and joint diseases have been described both in synoptic form and on the basis of original materials (Franceschetti, 1946; Sorsby and Gormaz, 1946; Edström, 1937), but aetiological and pathogenic outlines have not been drawn.

The incidence and symptomatology of concurrent eye and joint diseases will first be recapitulated in brief, the main stress being laid on the features relevant to the present investigation.

The medical ("rheumatic") joint diseases complicated by eye symptoms (Table I) comprise 2 groups: acute diseases (rheumatic fever, gonorrhoeal arthritis, and simple, urethritic polyarthritis or Reiter's disease) and chronic diseases (primary chronic polyarthritis, Still's disease, and ankylopoietic spondylo-arthritis or Pierre Marie-Strümpell-Bechterew's disease). Uratic arthritis is —with some reservation—included among the acute diseases.

TABLE I

Incidence (per cent.) of eye symptoms complicating joint diseases

	Conjunctivitis	Iritis	Sicca-syndrome
Acute joint diseases			
Rheumatic fever	5–10	4–5	—
Gonorrhoeal arthritis	10	5	—
Reiter's disease	80	10	—
Uratic arthritis	—	2	—
Chronic joint diseases			
Primary progressive chronic polyarthritis	—	2–5	10
Still's disease...	—	20	—
Ankylopoietic spondylo-arthritis ... (Bechterew-Strümpell-Marie)	—	15–50	—

In Denmark the most frequent form of joint disease is rheumatic fever with about 4,000 fresh cases annually. Next in frequency follows primary chronic polyarthritis with 3-400 fresh cases annually and a total of about 8,000 cases. All the other joint diseases are far less frequent. Gonorrhoeal arthritis is a rare phenomenon since the introduction of sulphonamide and penicillin treatment. Before the era of chemotherapy 1 to 5 per cent. of the gonorrhoea cases were complicated by joint diseases (Heerfordt, in 1909, collected 191 joint cases among 2,300 patients with gonorrhoea). The triad of polyarthritis, non-specific urethritis, and conjunctivitis (Reiter, 1916) has been observed with increasing frequency in many countries during and after the second world war (Skydsgaard, Haar, Paronen, whose material is the largest so far) and may be found also in women (Zewi found 6 women among 10 cases in 1947). In Paronen's abundant Finnish material (1948), comprising 325 cases of Reiter's disease, the syndrome was complete in 70 per cent., while joint symptoms were present in 98 per cent., eye symptoms in 90 per cent., and urethritis in 79 per cent. Initial dysentery-like gastro-enteric symptoms were found in 96 per cent.

Still's disease (1897) is a variety of chronic polyarthritis (periarthritis) affecting children, chiefly girls. In addition to chronic iridocyclitis, often with zonular keratitis, the disease is associated with polyadenitis and enlargement of the spleen, and the general condition is affected (Friedländer, Ejler Holm, Blegvad, Poulsen).

Uratic arthritis and ankylopoietic spondylitis being also fairly rare, the joint diseases of the most immediate importance in this connexion are rheumatic fever, primary chronic polyarthritis, and Reiter's disease.

All the above joint diseases, except uratic arthritis, may be included under the heading of infective arthritis. The arthrosis group, on the other hand, is not associated with eye symptoms. The articular symptomatology is characterized by being polyarticular. Ankylopoietic spondylitis begins in the sacro-iliac joints, whence it proceeds up through the joints of the vertebral column.

The eye symptoms in these joint diseases comprise in the main three distinct groups: (1) endogenous conjunctivitis, including episcleritis and scleritis, (2) iritis and iridocyclitis, and (3) the sicca-syndrome. In rare cases may be added optic neuritis and ocular palsies.

Iritis may be found in association with any one of the above seven joint diseases, at frequencies varying from 2 to 50 per cent. It is most rare in association with uratic arthritis (2 per cent.), primary chronic polyarthritis (2 to 5 per cent.), gonorrhoeal

arthritis and rheumatic fever (4 to 5 per cent.), but more frequent in Reiter's disease (10 per cent.) and ankylopoietic spondylitis (15 to 50 per cent.) (Comroe, Heerfordt, Paronen). The nature of the iritis in the acute joint diseases is chiefly acute, serous, with no essential characteristic, and in the chronic diseases chiefly chronic, though with acute exacerbations. In ankylopoietic spondylitis there is found an abundant exudation of fibrin into the anterior chamber. Still's disease may be associated with zonular keratitis.

Conjunctivitis occurs as a characteristic symptom only in the acute joint diseases, ranging in frequency from 10 to 80 per cent. (80 per cent. in Reiter's disease, 10 per cent. in gonorrhoeal arthritis, and 5 to 10 per cent. in rheumatic fever). Clinically it may have the form of a more or less superficial phlyctenular conjunctivitis or episcleritis (Heerfordt's subconjunctivitis epibulbaris) or a more diffuse bilateral conjunctivitis with limited secretion.

The sicca-syndrome (Sjögren's disease) is a characteristic occurrence only in primary chronic polyarthritis, with a frequency of 10 per cent. (Stenstam and Stig Holm, 1947). The clinical picture, described in detail by Sjögren (1933-40) and placed in relation to Plummer-Vinson's syndrome and ariboflavinosis (Godtfredsen, 1947) will not be discussed further. It should be remembered, however, that the disease is a generalized systemic affection of the secretory structures in the upper respiratory and alimentary tracts, lacrimal glands, pancreas and vaginal glands, with humoral changes (hyperglobulinaemia). The symptomatology is characterized by keratoconjunctivitis sicca, xerostomia, atrophic rhinitis, histamine-refractory achylia and desquamatory colpitis.

Even though from 2 to 50 per cent. of the joint diseases mentioned here are complicated by different eye symptoms, the total number of cases is rather limited, because the frequently occurring joint diseases most rarely show eye complications, whereas the reverse is the case for the rarer joint diseases (ankylopoietic spondylitis, Still's disease, and Reiter's disease). However, in the Eye Department of the Municipal Hospital, Copenhagen, we recently found that by systematic fractional urine examination ("two- or three-tube test") with inspection for fibres in all iritis cases we may discover a number of otherwise overlooked cases of Reiter's disease. Likewise the ophthalmologists will no doubt diagnose a greater number of ankylopoietic spondylitis cases by bearing this disease in mind when seeing iritis patients who have difficulty in pushing the chin forwards to the chin support of the slit-lamp, owing to the reduced mobility of the cervical part of the vertebral column.

PATHOGENESIS

The pathogenesis of the joint diseases mentioned in the present paper, is by no means fully elucidated, and there is no agreement in the literature. The most current views (Comroe, Cecil) are those summarised below.

Rheumatic fever is presumably an allergo-toxic reaction to infection with haemolytic streptococci, a hypothesis that is supported by the antistreptolysin titre, which is increased in 80 per cent. of the cases (> 200) (Kalbak; Winblad). In gonorrhoeal arthritis there is found gonococcaemia, and cultivation of gonococci from synovial fluid was performed before the gono-complement fixation reaction became positive. Reiter's disease, which originally was supposed to be due to a spirochaete, is still aetiologically obscure. The most recent literature ventilates the possibility of a virus, which, however, it has not yet been possible to cultivate. Reiter's disease often has an initial gastro-enteric stage, after which the characteristic triad manifests itself, probably released by an allergo-toxic agent. In uratic arthritis the essential feature is the pathological purine metabolism with increased serum uric acid values, and thus the pathogenesis differs from those of the other joint diseases. As for the three chronic joint diseases the aetiology is unknown, but is presumably infective and possibly—like Reiter's disease—of a virus nature with an allergo-toxic pathogenesis. Constitutional, possibly endocrine factors, are likely to play a part (Lövgren, 1945). This may explain the pronounced sex difference: primary chronic polyarthritis and Still's disease are most frequent among women, whereas Reiter's disease and ankylopoietic spondylitis are most frequent among men (Paronen; Sorsby and Gormaz).

In primary chronic polyarthritis 10 per cent. of the cases have increased antistreptolysin titre, which is only slightly above the normal findings (6 per cent., Kalbak). The agglutination test for haemolytic streptococci, on the other hand, yields increased values in 80 per cent. (Kalbak, 1946), a finding which has supported the theory of the aetiological importance of haemolytic streptococci. However, the most recent investigations (Wallis, 1947) seem to show that the agglutination reaction is not specific, but a more general indication of an abnormal serum instability (similar to the conditions which may give a positive Takata reaction). The agglutination test gives a negative reaction in ankylopoietic spondylitis.

Common to the above joint diseases—except uratic arthritis—is thus the fact that the pathogenesis seems to be an allergo-toxic reaction to a primary infectious agent, the aetiology of which is

clear for rheumatic fever (haemolytic streptococci) and gonorrhoeal arthritis. The aetiology of the other joint diseases is obscure; the possibility of a virus infection is present.

The clinical picture and the course of these joint diseases with and without associated eye signs being otherwise alike (Stenstam; Holm) we may suppose that the pathogenesis of the eye signs is the same as that of the joint symptoms, being thus of an allergo-toxic nature. This hypothesis is supported by the clinical picture of the eye symptoms. Phlyctenular conjunctivitis, or episcleritis, corresponds exactly to the eye signs in well-known allergic conditions, such as serum disease, sulphonamide allergy and tuberculin allergy. The histopathological picture of the phlyctenules is the same in these diseases, presenting an aggregation of polymorphonuclear leucocytes, small lymphocytes, and epithelioid cells, sometimes polynuclear, reminiscent in structure of Aschoff's nodules in the myocardium and the rheumatic nodules in the skin demonstrated in rheumatic infection (Edström and Osterlind). The iritis attending the joint disease resembles the monosymptomatic primary iritis, the aetiology of which is to an increasing extent believed to be allergo-toxic (Duke-Elder, 1947). Bjorn Foss' experimental work on anaphylactic iritis (1947) tends in the same direction. The pathogenesis of the sicca-syndrome may vary. Both hormone-biological factors and avitaminosis may play a part; but in the great majority of the sicca cases associated with primary chronic polyarthritis, the infective pathogenesis with an allergo-toxic reaction is the most likely one.

Discussion

That the eye may be affected in the joint diseases mentioned above is probably due to various factors, of which a few will be pointed out. It has been shown that the blood-synovial barrier of the joints and the blood-aqueous barrier of the eye exhibit the same conditions of permeability for the substances involved in the inflammatory processes. In experimental streptococcaemia in animals (Angevine and Rothbard, 1940) the ciliary processes of the eye and the synovia of the joints were the places where the streptococci by preference elicited inflammatory changes.

Human clinical medicine does not, however, bear out the animal experimental findings. Thus among 72 cases of streptococcaemia, Sylvest (1946) found 6 with eye signs (iritis, vitreous body abscess, and conjunctivitis), but without joint symptoms, which were present in one-third of the remaining cases.

The primary infective agent is unknown in several of the concurrent eye and joint diseases reported in this paper, but

known in gonorrhoeal arthritis, and is presumably haemolytic streptococci in rheumatic fever (where 80 per cent. had increased streptolysin-titre). For primary acute iritis without joint symptoms, on the other hand, the significance of haemolytic streptococci is doubtful since the antistreptolysin titre does not here differ from the normal (Björk, 1947).

The supposed allergo-toxic processes resulting in concurrent eye and joint diseases seem to bear no relation to allergic constitution and heredity, since these patients do not to any conspicuous extent present otherwise well-known allergic symptoms, such as vasomotor rhinitis, hay fever and urticaria.

It should be pointed out that many of the above concurrent eye and joint diseases have a more generalized character, presenting signs in other organs or systems as well, *e.g.*, the cardiac complications in rheumatic fever, the generalized glandular affection in Sjögren's syndrome, the polyadenitis and the splenic enlargement in Still's disease, the urethritis in Reiter's disease, etc. This generalized symptomatology has clinico-topographic points of resemblance to various characteristic diseases where not only the eyes and the joints are affected, but also the skin and the mucous membranes around the orifices of the body—the so-called pluri-orificial location (with conjunctivitis, stomatitis, affection of the external genitalia, *e.g.*, balanitis, vulvo-vaginitis)—and where the pathogenesis is supposed to be allergo-toxic on an infective basis.

The most important diseases with cardinal signs constituting a more or less constant tetrad of signs from eyes, joints, skin, and oral and genital mucous membranes have been set out in Table II, grouped according to the supposed aetiology (bacteria, virus, unknown, intoxication). The frequently protean clinical pictures will not be discussed in detail, but brief mention may be made of the following facts. Stevens-Johnson's syndrome (1922) is a special form of manifestation of exudative erythema multiforme* with concurrent skin exanthema of cockade-like eruptions increasing to bullous dermatitis, as well as stomatitis, conjunctivitis, and balanitis, more rarely polyarthritis (Edmund: Jersild; Ustvedt, 1948). A similar clinical picture is met with in the exceedingly rare Behcet's syndrome (Tage Jensen, Bechgaard), where, however, the skin lesion may be more of the character of erythema nodosum. Furthermore there is found a recurrent iritis with hypopyon, aphthous stomatitis, and genital affection. Analogous pictures are seen when foot-and-mouth disease affects humans (Bojlén). Acute disseminated erythematous lupus is likewise a rare and severe disease (V. Mortensen; Cordes

* Recently discussed by J. E. Wolff (1949, in *Brit. J. of Ophthal.*, 33, 110.

TABLE II

Diseases with concurrent symptoms from eyes, joints, skin and mucous membranes

	Eyes	Joints	Skin	Mucous membranes (stomatitis, balanitis)
Virus diseases or obscure aetiology				
Reiter's disease	+	+	+	+
Stevens-Johnson syndrome ...	+	(+)	+	+
Behcet's syndrome	+	(+)	+	+
Foot-and-mouth disease	+	?	+	+
Acute disseminated erythematous lupus	+	+	+	+
Measles, chicken-pox	+	(+)	+	+
Bacterial diseases				
Gonococcal sepsis	+	+	(+)	+
Streptococcal sepsis	(+)	+	+	+
Intoxications				
Sanocrysin, arsenicals	+	(+)	+	+
Serum sickness	+	+	+	+

(+) means less significant.

and Aiken, 1947) with a polymorphous picture comprising the skin lesion, polyarthritis, lymphadenitis, endocarditis and pluri-orificial ulcerative mucosal affections.

Gonococcaemia and streptococcaemia have already been mentioned. The morphology of the exanthemata may here vary a great deal. Intoxications by heavy metallic salts, notably sanocrysin (*cf.* Sundelin, 1941) and arsenicals (arsphenamine) may cause exfoliative dermatitis, endogenous conjunctivitis, stomatitis, and varying joint symptoms, very much like exudative erythema multiforme (Edmund). The disseminated exanthema, polyarticular lesions, and mucosal symptoms of serum disease are well known.

CONCLUSION

It is hardly possible to draw any definite conclusions, because our knowledge of many of the clinical pictures mentioned above is still rather limited. But it appears from the present clinical

analysis that a group of the rheumatic joint diseases, which—except uratic arthritis—all belong to the type of infective arthritis, are to a certain extent associated with eye symptoms, chiefly of an allergo-toxic nature. The eye and joint disease may be presumed to have the same aetiology and pathogenesis, where either a definitely known or a supposed primary bacterial (or virus) infection releases the allergo-toxic symptoms. The many clinical points of resemblance to various generalized diseases located on the skin, the pluri-orificial mucous membranes, and the joints, where allergo-toxic pathogenesis is certain or likely, bear out the hypothesis of an allergo-toxic pathogenesis of concurrent eye and joint diseases in a more restricted sense.

The therapeutic consequences of the above lines will not be discussed further in this place. The underlying bacterial diseases respond to treatment with sulphonamide and penicillin, whereas this has no influence on the supposed virus diseases. Although histamine is only symptomatic of the allergic process, it may be of interest to attempt an anti-histamine treatment (benadryl, pyribenzamine, and antistine). This has been tried on iritis without joint symptoms (Lemoine, 1947) with encouraging results, which, however, need further testing. The favourable response of sanocrysin intoxications to BAL (Cohen, 1947; Edström, 1948) might perhaps prompt one to the use of BAL against some of the related diseases mentioned here.

SUMMARY

A clinical analysis is given of the incidence and symptomatology of concurrent eye and joint diseases. The medical joint diseases which are complicated by eye symptoms (phlyctenular conjunctivitis, scleritis, iritis, and kerato-conjunctivitis sicca) all belong to the type of infective arthritis, partly acute and partly chronic (rheumatic fever, gonorrhoeal arthritis, Reiter's disease, Still's disease, and ankylopoietic spondylitis). The pathogenesis is presumably the same for the eye disease and the joint disease, being probably an allergo-toxic reaction to a primary bacterial or virus infection. This hypothesis is borne out by clinical points of resemblance to various generalized diseases affecting joints, skin and pluri-orificial mucous membranes (conjunctivitis, stomatitis, and affection of external genitals), where an allergo-toxic pathogenesis is certain or likely—Stevens-Johnson's syndrome, Behcet's syndrome, foot-and-mouth disease, serum disease, acute disseminated erythematous lupus, and intoxication by heavy metallic salts, notably sanocrysin and arsenicals.

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OX VITREOUS HUMOUR. 2.—HYALURONIC ACID RELATIONSHIPS*

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INTRODUCTION

This paper is a report of experiments bearing on the state of hyaluronic acid within the ox vitreous humour and the inter-relationships, both chemical and structural, between it and the soluble and insoluble proteins of the humour. Isolation of hyaluronic acid from ox vitreous humour by Meyer and Palmer (1934) naturally gave rise to the idea that this viscous polysaccharide is concerned with the maintenance of the vitreous body. Meyer and Palmer isolated it in a concentration of about 0·05 per cent. from ox vitreous humour filtrate and although Meyer, Smyth and Gallardo (1938) showed that the humours of other animals did not contain so much, yet it is obviously an important constituent of all that have been so far examined. In the ox vitreous humour there is more hyaluronic acid than soluble or insoluble protein. Table I gives values for the concentration of hyaluronic acid and the proteins of the vitreous humours of ox and man and demonstrates the great dilution in which they occur.

TABLE I.—COMPOSITION OF VITREOUS HUMOUR

Vitreous humour	Ox	Man	Ox	Man
	mg/100 ml.		mg/single humour	
Total nitrogen	22–24[1]	23·5[2]	3·9–4.3	0·9
Soluble protein	39–43[1]	20–40[3]	7–8	0·78–1·56
Residual protein	11–16[3]	—	2–3	—
Hyaluronic acid, calculated from hexosamine ...	41[3]	9·9[2]	7·5	0·38
,, ...	—	11·5–19[3]	—	0·44–0·75

The volume of a single ox vitreous humour is taken as 18 ml.
The volume of a single human vitreous humour is taken as 3.9 ml. (Tab. Biol. 1947).
[1]Krause (1934).
[2]Meyer, Smith and Gallardo (1938).
[3]Own results.

* Received for publication, September 11, 1948.

The vitreous humour has been described in many different ways; histologists, physical chemists and ophthalmologists each have a different approach to the problem, which is basically to account for the stability of a structure which contains such low concentrations of its constituents. A study of the residual protein of the ox vitreous humour by Pirie, Schmidt and Waters (1948) led them to consider that the picture given by the histologists most nearly fitted their biochemical findings. According to this view, the vitreous humour is a tissue made up of a network of fibrils which are the prolongations of cells and this network is permeated by a viscous fluid, or jelly, which easily flows out of it. Pirie, Schmidt and Waters found that hydrolysis of the fibrillar protein by enzyme preparations containing collagenase caused liquefaction of the humour. This protein, however, occupies only a minute part of the total volume of the humour which is made up of a viscous solution or jelly of hyaluronic acid, soluble proteins derived from the blood and substances of small molecular weight.

Breakdown of this may also be expected to cause pathological changes in the humour. For example, it seems possible that disaggregation of the hyaluronic acid to a non-viscous form might also lead to disorganisation of the fibrillar network, perhaps with production of visible opacities, such as those seen in senile degenerations of the humour. It is well known that substances diffuse through the vitreous humour *in vivo* with extreme slowness. Haemorrhages remain localised for long periods and von Sallmann, Meyer and di Grandi (1944) found that penicillin injected intra-vitreally diffused through only one-third of the volume of the humour in 6 hours. This lack of spread may be due either to the way in which the fibrillar protein is laid down, or to the inhibiting effect on the diffusion of large molecules by the hyaluronic acid jelly. Probably both play some part and one might therefore expect that a change in the state of either would be reflected in changes, both in the state and in the behaviour of the vitreous humour. As a first step in the experimental consideration of these inter-relations, a study has been made of the state of hyaluronic acid in the normal ox vitreous humour and of the effect of hyaluronidase, the enzyme system that disaggregates and hydrolyses hyaluronic acid, on the behaviour of ox vitreous humour *in vitro*.

The state in which hyaluronic acid exists in the tissues and fluids of the body is not yet clear. Evidence derived from electrophoresis seems to show that it is not combined with protein at the pH of the body, but exists free, presumably as an ion. For example, Blix (1940) found that electrophoresis of filtered, dialysed and concentrated ox vitreous humour caused the hyaluronic acid

to migrate in the electric field faster than any of the proteins present. Meyer and Chaffee (1940) found that the hyaluronic acid of a viscous fluid obtained from a tumour behaved in the same way, yet many workers have been impressed by differences in physical properties between the native fluids of the body and hyaluronic acid solutions of comparable strength. For example, the viscosity of the tumour fluid studied by Meyer and Chaffee was far greater than the viscosity of solutions of hyaluronic acid of equal strength, perhaps showing that hyaluronic acid is combined with protein in the native fluid. On the other hand, it is possible that this difference in the viscosity of the native fluids and of solutions of hyaluronic acid isolated from them lies only in the different degree of aggregation of hyaluronic acid in the two situations.

Blix and Snellmann (1945) found that hyaluronic acid prepared from different sources had very different particle lengths, or degrees of molecular aggregation and that even hyaluronic acid from a single source might be polydisperse. For example, the material prepared from ox vitreous humour had particle lengths varying from 1,000 A° to 4,800 A°, judging from viscosity measurements. Hadidian and N. W. Pirie (1948) have recently isolated highly aggregated hyaluronic acid from umbilical cord with a relative viscosity greater than that of any previous preparations and they speak of hyaluronic acid as a family of substances differing slightly in architecture and greatly in particle size.

Consideration of the state of hyaluronic acid in the vitreous humour may, therefore, be directed to determine whether it is free or combined with protein and whether it is highly aggregated and, therefore, possibly immobile within the humour structure, or relatively disaggregated and freely diffusible. Meyer (1947) has suggested that hyaluronic acid is formed in the ciliary body and circulates in the vitreous humour, finally escaping into the aqueous humour, where it is disaggregated by hyaluronidase. Knowledge of the state and mobility of hyaluronic acid in the vitreous humour should help to evaluate these very interesting suggestions.

METHODS

State of aggregation of hyaluronic acid. Aggregated hyaluronic acid gives a fibrous precipitate with protein in dilute acid or acid acetone. Disaggregated hyaluronic acid gives either a flocculent precipitate or cloud under these conditions. This difference in precipitability has been used to estimate the disaggregating, or mucinase, effect of hyaluronidase and other systems by Robertson, Ropes and Bauer (1940). In the absence of protein, hyaluronic acid is not precipitated by dilute acid, but comes down with acetone. Aggregated hyaluronic acid gives a fibrous precipitate and disaggregated a flocculent one. I have used the change in type of precipitate with acid acetone as a qualitative test for the degree of aggregation of hyaluronic acid. The presence of 75 per cent. of the aggregated

form masks the presence of 25 per cent. of the disaggregated acid, but the test is sufficient to show any major disaggregation. The solution to be tested is acidified with dilute acetic acid and added to 2-3 vol. acetone. A fibrous clumped precipitate in a clear fluid is characteristic of aggregated hyaluronic acid, while a cloud or flocculent precipitate shows that the acid has been disaggregated.

Hexosamine was estimated by the method of Elson and Morgan (1933) and total nitrogen by micro-Kjeldahl followed by distillation and titration, using the apparatus described by Markham (1942). Total carbohydrate was estimated by the orcin colorimetric method described by N. W. Pirie (1936); this estimates the glucuronic acid but not the hexosamine part of the hyaluronic acid molecule.

MOBILITY OF HYALURONIC ACID THROUGH VITREOUS HUMOUR

Ox vitreous humour contains both proteins and hyaluronic acid in solution. Friedenwald and Stiehler (1934) found that all soluble organic material could be removed from a humour by prolonged washing in saline. It is, therefore, possible for hyaluronic acid to diffuse through and escape from the humour, but whether it does so combined with protein, or as an independent entity is not known. An attempt to answer this was made by analysing the material that stayed within the humour after varying times of washing. If protein and hyaluronic acid diffused out independently, then the composition of the material remaining should vary according to the time of washing.

Ox vitreous humours taken out of the eye ½—2 hours after death were suspended in water or saline for varying periods in the ice chest. The washing fluid was changed each day and finally the vitreous humour was filtered and the filtrate precipitated with acid acetone. The composition of this precipitate was compared with that from an ox vitreous humour filtered immediately after removal from the eye. In this way the rate of escape of protein and of hyaluronic acid could be roughly estimated. In some cases the composition of the precipitate from the washing fluid was also investigated. The first wash waters contained considerable salt and gave a flocculent precipitate with dilute acetic acid, indicating the presence of protein and hyaluronic acid which precipitate as a mucin compound in the dilute acid. The later wash waters contained no salt, no mucin and only traces of material precipitable by acetone. In contrast with this, the filtrates of fresh humours gave acetone precipitates with a carbohydrate content of 9—12 per cent., while filtrates of well-washed humours gave acetone precipitates with a carbohydrate content of 14—38 per cent. The acetone precipitate from the filtrate of a fresh humour after dialysis in a cellophane sac had a carbohydrate content of 14 per cent. This shows that the protein in the ox vitreous humour washes out more easily than the carbohydrate hyaluronic acid. This was further demonstrated by an experiment in which a single vitreous humour was suspended in water for

eight days, the water being changed each day. The wash waters were combined, concentrated and then added to acid acetone. The precipitate was centrifuged off, dried, weighed and its carbohydrate content was determined. On the eighth day the vitreous humour was filtered and the filtrate precipitated with acetone and the precipitate analysed in the usual way. The acetone precipitate from the collected wash waters weighed 17·8 mg. and contained 7·1 per cent. carbohydrate, while the acetone precipitate from the filtrate weighed 9·2 mg. and contained 20·4 per cent. carbohydrate. Table II gives the analysis of the acetone precipitates from the

TABLE II.—COMPOSITION OF ACETONE PRECIPITABLE MATERIAL FROM THE FILTRATE OF OX VITREOUS HUMOUR AFTER VARIOUS TIMES OF WASHING THE HUMOUR IN H_2O.

Washing time days	Wt. Precipitate from 1 humour mg.	Total N %	Total Carbohydrate (Glycuronic Acid — as glucose) %	Hexosamine %
0	19·8	—	10·1	—
0	20·7	—	9·2	—
0	—	6·7	12·6	11·3
0	—	6·5	—	7·6
3	15·9	—	14·6	—
9	6·5	—	14·6	—
14	>4·0	—	19·0	—
22	3·6	7·0	24·0	19·5
28	7·6	7·5	38–43	24·0
approx. 1 month	3·7	7·1	—	12·1
"	—	6·3	23·0	24·4
"	—	6·4	19·5	26·6
Dialysed fresh filtrate	15·9	7·9	14·6	16·6
Hyaluronic acid Meyer & Palmer (1936)	—	3·37	46·8	43·1

vitreous humours after various washing times and shows that there is a progressive increase in the carbohydrate content of the material remaining within the humour. The same progressive increase in the carbohydrate content of the relatively immobile material occurred when the vitreous humour was washed in 0·9 per cent. saline rather than in water.

The ash content of the acetone precipitate from fresh humours was 13—17·7 per cent. while that from a washed humour was 4·9 per cent. Calculation, on an ash free basis, of the protein and hyaluronic acid contents of these precipitates shows that the precipitate from a fresh humour has roughly 36 per cent. protein and 25 per cent. hyaluronic acid and the precipitate from a washed humour has 31 per cent. protein and 50 per cent. hyaluronic acid. This means that these experiments have not shown that protein and hyaluronic acid wash out quite independently of each other, but have demonstrated that they are relatively independent and that no compound similar to a mucin exists in the vitreous humour.

Two further *points of interest arise from these experiments.* The washing fluids from the vitreous humours always gave flocculent precipitates, either with acid alone or with acid acetone, whether the volume of the fluid was large or purposely kept small. This means that under the conditions of the experiment, aggregated hyaluronic acid does not diffuse out of the vitreous humour. All that diffuses is already disaggregated. The instability of aggregated hyaluronic acid is well known and Robertson, Ropes and Bauer (1940) showed that vitreous humour filtrate contained a disaggregating system, which they identified as ascorbic acid. It seems probable that gradual disaggregation of the hyaluronic acid goes on during washing. The material which stays within the washed humour and can be filtered out is always in the aggregated form giving a fibrous precipitate with acid acetone. This supports Meyer's idea of a circulation of hyaluronic acid in the eye with final escape through the aqueous humour of the disaggregated material.

A second point of interest is that the filtrate from a washed vitreous humour is not uniform in composition. After 7—10 days in repeated changes of distilled water, ox vitreous humour swells to 2—4 times its original size. Such swelling has already been described by Goedbloed (1935). I found that the filtrate from such swollen humours varied in composition, the first part, coming presumably from the outer part of the humour mass, being *almost* free from precipitable material and the last 5—10 ml. containing highly aggregated hyaluronic acid. This implies either that there is an internal structure of the vitreous humour, or that the jelly

of hyaluronic acid and protein is broken down gradually, the outer parts being washed away first. The very unstable character of the vitreous humour jelly makes this second explanation seem improbable and I think that this experimental finding is in favour of the view that there is an internal network which impedes to a certain extent the movement of large molecules.

INFLUENCE OF STRUCTURAL PROTEIN ON STATE OF HYALURONIC ACID

The action of hyaluronidase on the vitreous humour in the eye and excised from the eye and on the vitreous humour filtrate was studied in order to see whether the presence of the vitreous structure influenced in any way the action of the enzyme on the contained hyaluronic acid. The enzyme preparations were injected into the vitreous humour with a hypodermic syringe and the eyes, or the extracted humours or filtrates, were then incubated at 37° for varying times. Humours injected with saline were incubated to control the spontaneous disaggregation of hyaluronic acid. After incubation the vitreous humours were filtered directly into acid acetone in order to stop enzyme action and get immediate precipitation of mucin. The activity of the enzyme was judged by the type of precipitate obtained, a fibrous precipitate showing that the hyaluronic acid was still aggregated and a flocculent precipitate showing that the enzyme had disaggregated it. In some cases the insoluble residues from the humours were washed, dried and weighed in order to measure whether hyaluronidase had any effect on the residual protein.

Table III gives the results of these experiments and shows that in no case did hyaluronidase liquefy or have any grossly visible effect on the vitreous humour. Blix (1946) has already noted that hyaluronidase does not liquefy vitreous humour. Enzyme preparations that disaggregated hyaluronic acid instantly in the filtrate took a long time to disaggregate it when it was retained in the vitreous humour structure. The enzyme was slowed down even more when acting on the vitreous humour in the eye. This difference in the rate of action of hyaluronidase inside and outside the vitreous humour is probably due to the slow rate of diffusion of the enzyme through the vitreous body. If an injection of enzyme is made into the centre of an intact extracted humour contained in a small pot, the injected enzyme can be seen as a small bubble of different refractive index for several hours after injection. The vitreous humour structure prevents rapid diffusion of substances through it and in this way the structural protein influences the state of hyaluronic acid in the humour and tends to maintain it in the aggregated state.

TABLE III.—EFFECT OF HYALURONIDASE ON OX VITREOUS HUMOUR

Exp: No.	Vitreous Humour preparation	Enzyme prep: injected	Time at 37° hr:	Gross effect	Acetone ppt: from filtrate	Residue Wt: mg.
1	In ox eye	0·1 ml. *Cl. Welchii* preparation 500 v.r.u./ml.	1¾	none	fibrous	—
	Freshly extracted	,,	1½	none	flocculent	—
	Filtrate	,,	none	none	flocculent	—
	In ox eye	none	1¾	none	fibrous	—
	Freshly extracted	none	1½	none	fibrous	—
2	In ox eye	0·5 ml. of 1% Testis extract	15	none	fibrous	4·0
	Freshly extracted	,,	15	none	flocculent	2·6
	In ox eye	none	15	none	fibrous	4·0
	Freshly extracted	none	15	none	fibrous	3·0
3	In ox eye	0·2 ml. Testis preparation 96 v.r.u./ml.	17	none	flocculent	3·0
	In ox eye	none	17	none	fibrous	3·9

One viscosity reducing unit (v.r.u.) of hyaluronidase is that concentration of enzyme that will reduce the viscosity of a standard substrate preparation to a level halfway between its original value and that of the solvent employed in 20 minutes, McClean (1942).

A further demonstration of this came from a study of another disaggregating system. Ascorbic acid, which is present in the normal vitreous humour in a concentration of 50 mg./100 ml. filtrate (Robertson, Ropes and Bauer, 1941), can disaggregate hyaluronic acid. This action is catalysed by copper, and addition of a small amount of copper to the filtrate of the ox vitreous humour caused immediate disaggregation of the hyaluronic acid. If, however, the same amount of copper was injected into the vitreous humour, no disaggregation occurred, even after 12—20 hours' incubation at 37°. This is probably because the copper combines with the structural protein and so becomes non-diffusible and inactive as a catalyst. Here again the presence of the structural protein has an influence on the state of hyaluronic acid.

INFLUENCE OF AGGREGATED HYALURONIC ACID ON DISSOLUTION OF STRUCTURAL PROTEIN BY COLLAGENASE PREPARATIONS

Pirie, Schmidt and Waters (1948) showed that enzyme preparations from *Cl. Welchii* containing collagenase liquefied ox vitreous humour. They found that the liquefied humours always contained disaggregated hyaluronic acid. The enzyme preparations contained no active hyaluronidase, but were found to have 0·043 mg./ml. of Cu and this presumably acted as a catalyst for the disaggregation of hyaluronic acid by ascorbic acid in the liquefying humour. Table IV shows the disaggregating effect of the enzyme preparation and shows that disaggregation can be inhibited by addition of sodium diethyl dithiocarbamate which combines with copper and makes it catalytically inactive. Experiment 3 shows that the enzyme preparation does not disaggregate hyaluronic acid from umbilical cord unless ascorbic

TABLE IV.—DISAGGREGATION OF HYALURONIC ACID BY *Cl Welchii* COLLAGENASE PREPARATIONS

Expt. No.	Substrate	Saline added ml.	Enzyme added ml.	Time hr. 20°	Type of Acetone precipitate from filtrate
1	5 ml. ox vitreous humour filtrate	0·2	—	23	fibrous
	ditto	—	0·2	23	flocculent
2	2 ml. ox vitreous humour filtrate	0 1	—	5	fibrous
	ditto	—	0 1	5	flocculent
	ditto	—	0.1 − 0.05 ml. 0.5% sodium diethyl dithio-carbamate	5	fibrous
3	1·0 ml. 0·9% hyaluronic acid (umbilical cord)	—	0·05	3	fibrous
	1·0 ml. 0·9% hyaluronic acid (umbilical cord) + M/3000 ascorbic acid	—	0 05	3	flocculent
	1·0 ml. 0·9% hyaluronic acid (umbilical cord) + M/3000 ascorbic acid	—	—	3	fibrous

TABLE V.—EFFECT OF AGGREGATED HYALURONIC ACID ON COLLAGENASE ACTIVITY

The enzymes or other solutions were injected into the vitreous humours which were incubated overnight at 37° in the presence of toluene in small glass pots. 0·2 ml. 0.5 % sodium diethyl dithiocarbamate was used in experiments 1 and 2 and 0·3 ml. 1% in experiment 3. 0·3 ml. or 0·4 ml. collagenase containing 22 Q units of activity/ml. was used and 0·2 ml. testicular hyaluronidase containing 96 viscosity reducing units/ml.

Addition to vitreous humour	Gross effect	Type of acetone precipitate from filtrate	Weight of residue after filtration mg.
Saline	none	flocculent	3·6
Saline plus dithiocarbamate	none	fibrous	3·2
Collagenase ...	fluid	flocculent	none
Collagenase plus dithiocarbamate	mainly solid	fibrous	2·1
Saline	none	fibrous	3·8
Saline plus dithiocarbamate	none.	fibrous	3·4
Collagenase ...	half fluid	flocculent	2·2
Collagenase plus dithiocarb mate	quarter fluid	fibrous	2·6
Saline plus *dithiocarbamate*	none	fibrous	1·5
Collagenase ...	part liquid	part fibrous	2·0 (very fragile)
Collagenase plus dithiocarbamate	solid	fibrous	1·8
Collagenase plus dithiocarbamate plus hyaluronidase	part liquid	flocculent	1·8 (very fragile)
Hyaluronidase ...	solid	flocculent	3·0
Hyaluronidase plus dithiocarbamate	solid	flocculent	3·0

acid is added. Both copper and ascorbic acid must be present for disaggregation to take place.

Mixture of diethyl dithiocarbamate with the collagenase preparation before injection into the vitreous humour slowed down

the liquefaction of the humour and the digestion of the insoluble protein. This effect is not due to inhibition of collagenase by the dithiocarbamate as corneal collagen is dissolved by collagenase in its presence. It seemed probable that dithiocarbamate prevented disaggregation of hyaluronic acid in the humour, and that aggregated hyaluronic acid prevented the spread of the collagenase through the vitreous humour mass, and so slowed down liquefaction.

I tried to verify this assumption by determining whether the inhibition of liquefaction by dithiocarbamate could be nullified by hyaluronidase. The experimental results were not entirely clear-cut, but showed that on the whole the addition of hyaluronidase to a mixture of collagenase and dithiocarbamate increased the liquefaction of the humour. In these experiments it was difficult to adjust the time of incubation so that no spontaneous disaggregation took place and yet the added hyaluronidase had sufficient time to disaggregate all the hyaluronic acid throughout the humour. The earlier series of experiments with hyaluronidase (Table III) had shown that the enzyme only acted slowly in the intact humour. Table V gives the results of three typical experiments, showing the inhibitory effect of dithiocarbamate on liquefaction and the effect of hyaluronidase on this. The last column records the weights of the insoluble residues from the humours after complete filtration. These residues were washed by suspension in water overnight whenever this was feasible, but in some cases they were so flimsy that this could not be done, and they were dried without washing, which means that the dry weight is probably too big.

DISCUSSION

The results of the experiments reported in this paper show that the soluble proteins wash out of the vitreous humour more easily than the hyaluronic acid, but that hyaluronic acid cannot be completely separated from protein in this way. The experiments do not therefore rule out the possibility that a compound of hyaluronic acid and protein occurs, but suggest that, if this is so, it is unlike the mucin type of compound obtainable by co-precipitation of hyaluronic acid and protein in dilute acid, where the hyaluronic acid forms a small part of the molecule.

Although hyaluronic acid and the insoluble collagen-like protein of the vitreous humour do not seem to have any chemical relation in the humour, yet they do influence each other. Aggregated hyaluronic acid has a very large particle size, and the hyaluronic acid-containing jelly of the vitreous humour may be considered as

an unstable structure that inter-acts with the structure of the insoluble protein. Liquefaction of the insoluble protein is slowed down by the presence of aggregated hyaluronic acid, and disaggregation of hyaluronic acid is slowed down by the presence of the insoluble protein. Each structure tends to preserve the other, and it seems possible that pathological changes in one might also lead to change in the other.

These experiments have been made on ox vitreous humour only. Meyer, Smyth and Gallardo (1938) have shown that the amount of hyaluronic acid is 3—4 times greater in the ox than it is in other animals. Von Sallmann (1948) has found that injection of hyaluronidase into the rabbit's eye causes partial liquefaction of the vitreous humour, and that the spread of injected haemoglobin in rabbit vitreous humour is accelerated by hyaluronidase. There are therefore big species-differences in the structure and behaviour of the vitreous humour, but it is likely that, even in species that have less hyaluronic acid in their vitreous humour than the ox, one must take into account the structural inter-actions between the collagen-like insoluble protein and the hyaluronic acid jelly when considering the biological behaviour of the vitreous body.

Summary

1. Suspension of ox vitreous humour in water washes out protein and hyaluronic acid at different rates, and the analysis of the material remaining within the humour shows that there is no compound comparable to a mucin present in the humour.

2. Hyaluronidase acts more slowly within the vitreous humour than in the vitreous humour filtrate.

3. Collagenase preparations are inhibited by aggregated hyaluronic acid in the vitreous humour.

4. The conclusion is drawn that the presence of the insoluble structural protein of the humour may help to maintain aggregated hyaluronic acid, and that aggregated hyaluronic acid may help to maintain the structural protein.

I wish to thank Miss E. Bidwell for the collagenase preparation, and Dr. H. J. Rogers for the purified hyaluronidase.

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LEIOMYOMA OF THE IRIS*

Report of a Case

BY

KEVIN O'DAY

MELBOURNE

THE clinical and pathological diagnosis of tumours of the iris presents many difficulties. Because of their rarity it falls to the lot of few observers to have more than a passing acquaintance with them. Fear of their possible malignancy warps the judgment of the surgeon, and neither the clinician nor the pathologist approaches the problem with an unbiassed mind.

In 1943 Kahler, Wallace, Irvine and Irvine reported "the seventh case of leiomyoma of the iris." Following the lead of Verhoeff, several reported myomata of the iris and ciliary body were rejected because of insufficient histological proof. On the other hand, it is not unlikely that many cases have been wrongly labelled leuco-sarcoma (unpigmented melanoma) because their real nature was not apparent with the usual haematoxylin and eosin stain. Van Gieson's stain and Mallory's connective-tissue stain show that the tumour cells take the stain characteristic of

* This case was presented at a meeting of the clinical society, St. Vincent's Hospital, Melbourne, Victoria, Australia, on March 22, 1948. Received for publication, October 25, 1948

Some months ago I forwarded to you a report on a case of leiomyoma of the iris. Just recently, I have seen a report by E. C. Moulton, Senr. and E. C. Moulton, Jnr. from Fort Smith, Arkansas, in the *American Journal of Ophthalmology* for February, 1948 (31, 214) in which they report a similar case. They mention the presence of cataract, and make a suggestion similar to mine, that the growth appears in the region of the foetal fissure. I was unaware of their article when I sent my report to you.

muscle. With Mallory's phosphotungstic acid haematoxylin the fibrillary nature of the tumour is apparent. Dense fibrils appear to take their origin from each end of the cell and course for long distances through the tumour without anastomosing. They bear no resemblance to the delicate anastomotic network of processes from the cells of a melanoma.

Clinically they may appear as grey, vascular tumours sessile or pedunculated. They may give rise to hyphaema, or as in the following case to cataract. They may be slow-growing or show periods of activity. Their diagnosis is of more than academic interest as they are benign and can often be completely removed by an iridectomy. For this reason every unpigmented or lightly pigmented tumour of the iris should be treated conservatively or subjected to biopsy before deciding on the fate of the eye. In the following case a clinical diagnosis of unpigmented melanoma was made with some confidence, and the eye removed. The histological findings were those of a leiomyoma.

On 6/1/47 Mrs. A. McH., aged 65 years, complained that the sight in the right eye had been failing for the previous twelve months. The vision in the right eye was 6/36, and could not be improved. The vision in the left was 6/12 and improved to 6/6. There was a sessile, unpigmented grey tumour occupying nearly the whole of the outer lower quadrant of the right iris. The outer edge was hidden by the limbus. It was very vascular and surrounded by a gelatinous fringe spreading over the surface of the surrounding iris. At the margin of the pupil there was a little ectropion of the pigment epithelium. The edge of the pupil appeared to be lifted forward, bringing the posterior surface of the iris into view and revealing a radial band of atrophy of the pigment epithelium. The lens was opaque behind the tumour, and the opacity was spreading across the pupil, obscuring the details of the fundus. The tension was normal, and remained so after the pupil had been dilated with homatropine and cocaine. The pupil dilated almost fully, and there was little evidence of distortion where the tumour abutted on the pupil. The most probable diagnosis appeared to be an unpigmented melanoma (leuco-sarcoma). The absence of rigidity of the iris, and the atrophy of the pigment epithelium introduced an element of doubt. The vascularity of the tumour, and the lens opacity which appeared to be caused by it were thought to be in favour of the diagnosis of malignancy. Iridectomy was not considered because it was probable that the tumour had already infiltrated the ciliary body, so that removal would not be complete.

The eye was removed, fixed in Zenker's fluid, embedded in celloidin, and sections stained in haematoxylin and eosin, van Gieson, Mallory's connective tissue stain, Mallory's phosphotungstic acid haematoxylin and Wilder's reticulin stain. The sections showed a tumour (Fig. 1) extending from the pupil to the base of the iris and beginning to invade the ciliary body. It appeared to occupy the interstices of the iris, compressing the normal tissues rather than infiltrating them. The posterior surface of the iris was curved backwards, dimpling the lens where it had caused proliferation of the sub-capsular epithelium (Fig. 2), and destruction of the fibres beneath. The pigment epithelium

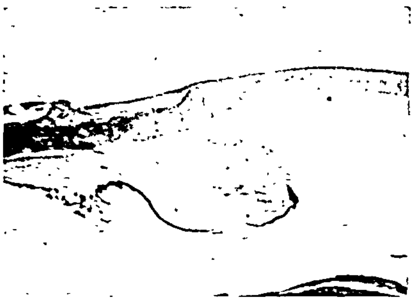

FIG. 1

Mallory's connective-tissue stain. The more darkly staining area is the compressed iris tissue.

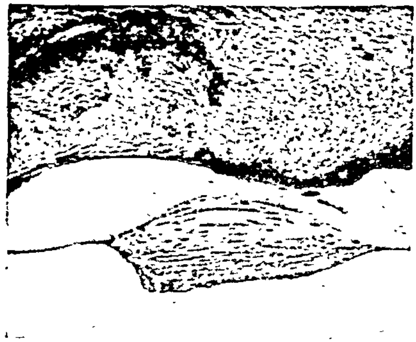

FIG. 2

Mallory's connective-tissue stain. Atrophy of pigment epithelium. Proliferation of subcapsular epithelium of the lens.

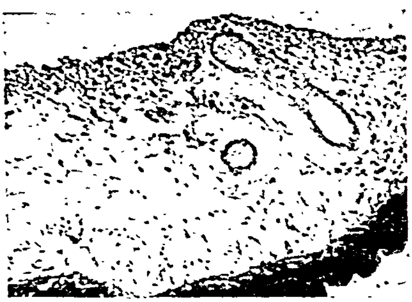

FIG. 3

Haem and eosin. section through the gelatinous fringe. Tumour cells growing along the anterior surface of the iris, and a large new vessel.

FIG. 4

Haem. and eosin. Base of the iris. Infiltration with round cells. Swollen tumour fibrils in the lower right-hand corner above the pigment epithelium.

of the iris had disappeared at the posterior limit of the curve. Anteriorly the tumour had compressed the normal iris tissue. There was no evidence that it was actually infiltrating this structure, but it had escaped through the openings of the crypts. Sections cut at the edge of the tumour showed a thin layer of tumour-cells spreading over the surface of the iris (Fig. 3), and accounting for the gelatinous fringe seen clinically. At the base of the iris there was evidence of a recent haemorrhage being absorbed in one of the crypts. Where the tumour was invading the ciliary body there was a collection of small round cells with some oedema (Fig. 4). The tumour was composed of bundles and

whorls of spindle-shaped cells ending in long fibrils (Figs. 5 and 6). The nuclei were rod-like and arranged in the so-called palisade formation. In some areas where the bundles were cut transversely (Fig. 6), many nuclei were to be seen in the one section. In others, the nuclei were very few in number, and the bundle composed mainly of fibrils. The chromatin of the large cylindrical nuclei was scattered in fine granules with one or two more dense aggregations. No mitotic figures were seen. Very little protoplasm could be seen surrounding the nuclei except in those cells lying near the dilator muscle. Here each end of the cell tapered off rapidly to a coarse fibril which could often be followed across several high-power fields. There was no evidence of any anastomosis with neighbouring fibrils. Its thickness did not always remain constant, and it would often present a marked fusiform dilatation at some distance from the nucleus. In the main mass of the tumour the amount of the protoplasm surrounding the nucleus was greatly reduced, and the fibrils appeared to split to surround it. The swelling of the fibrils was seen everywhere, even in the isolated bundles of cells creeping round the base of the iris to invade the ciliary body (Fig. 3). In cross-section it appeared as a circular homogeneous mass (Fig. 6). The cell body, fibril and dilatation stained a uniform pink with eosin, yellow with van Gieson, red with Mallory's connective-tissue stain, and a deep violet with the phosphotungstic acid haematoxylin, in contrast in the latter case with the red tinge of the violet of the connective tissue of the iris. Mallory's connective-tissue stain showed that the connective tissue in the section belonged to the compressed iris. There was little evidence of new formation of connective tissue between the tumour cells, and no reticulin. There were several large blood vessels in the tumour, and many fully formed capillaries with connective-tissue walls. None was embryonic in type. The pigment content of the tumour was small and confined to the compressed iris tissue, where chromatophores were present (Fig. 7). Pigment-laden cells, probably phagocytes, were present in large numbers in the spaces of the pectinate ligament in both angles. In the general picture seen with Mallory's connective stain, and with that of Wilder, it was obvious that the tumour had compressed the normal tissue, and if it had not found a way out through the crypts of the iris and through the loose tissue of the base of the iris, it would have become encapsulated thereby (Figs. 1 and 7). The compression of the superficial tissues of the iris was so marked that, when stained with haematoxylin and eosin, the cells of the anterior border layer formed a distinct line in the depth of the tumour right across the section (Fig. 6). The tumour had all the characteristics of a leiomyoma.

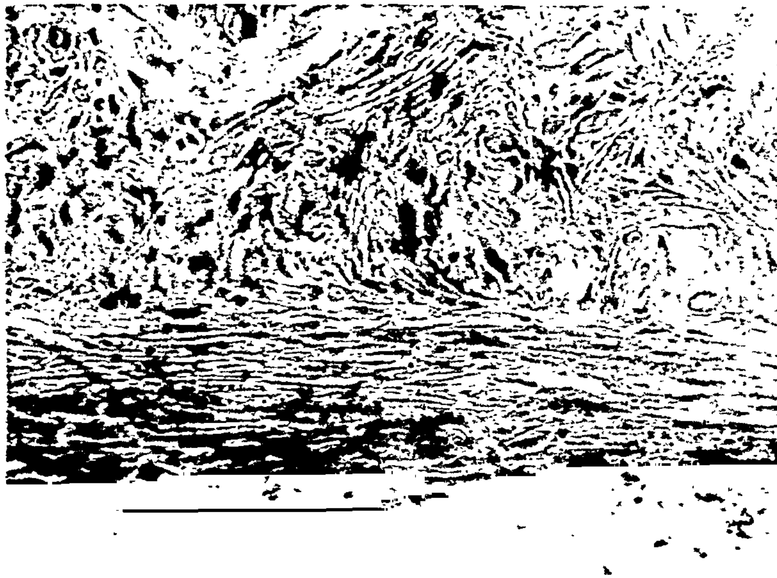

FIG. 5

Mallory's phosphotungstic acid. Posterior section of the iris. The pigment epithelium is at the lower edge.

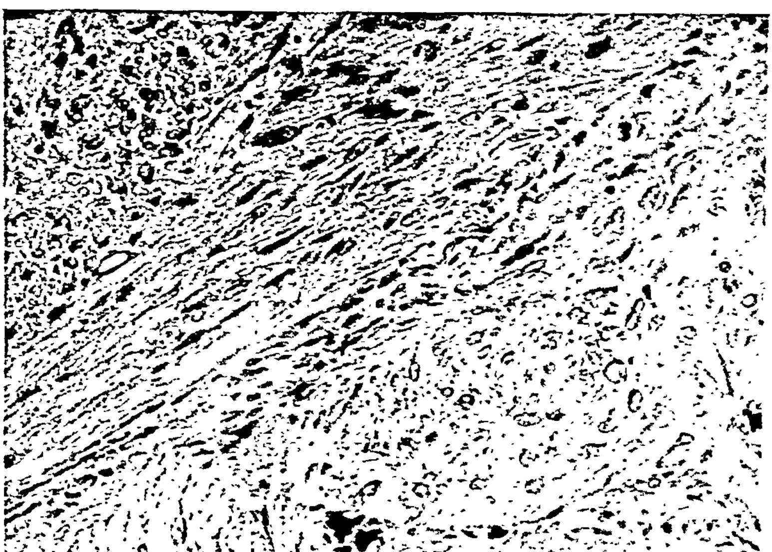

FIG. 6

Haem. and eosin. The anterior border layer runs from the lower left to the upper right-hand corner. The anterior surface is above this diagonal A transverse section of a bundle of fibrils in the lower right-hand corner shows many fibrils of varying thicknesses and few nuclei. Comparatively more nuclei are present in the upper left-hand bundle.

FIG. 7

Wilder's reticulin stain. Ectropion of pigment epithelium with tumour cells growing over it and also splitting it. Reticulin is apparent only in the compressed iris tissue. The tumour has reached the surface through the orifice of a crypt.

FIG. 8

Region of the sphincter on the side of the pupil opposite the tumour. Haem. and eosin. Atrophy of pigment epithelium. Proliferation of cells of dilator. Collection of chromatophores and pigment-laden phagocytes.

There was some atrophy of the pigment epithelium of the iris posterior to the sphincter muscle on the side of the pupil opposite the tumour (Fig. 8). This was associated with proliferation of the cells of the dilator muscle in that region. There was an abnormal appearance of chromatophores in the area, as if they were migrating forwards into the sphincter muscle. There were other round pigment-laden cells, probably phagocytes, in the vicinity, some in the space between the sphincter and the dilator, others on the posterior surface of the iris. This may have been an early nodule of tumour of the dilator muscle distinct from the main mass.

COMMENT

It is impossible to say from which muscle the tumour arose. Some sections appeared to show the cells of the dilator muscle elongating, gradually losing their pigment content, and merging into a general stroma of the tumour. Four factors call for special comment :—

1. The presence of haemorrhage. Van Duyse comments on this with the remark that intra-ocular haemorrhage in the presence of tumour does not necessarily indicate malignancy.

2. The presence of inflammatory exudate where the tumour was invading the ciliary body. In addition, an occasional ghost cell was seen along the posterior surface of the iris.

3. The presence of proliferation of the subcapsular epithelium of the lens due directly to the pressure of the tumour.

4. The presence of fusiform dilatations along the fibrils of the tumour. These receive no mention in the reports of Verhoeff, Frost, Ellett and Kahler *et al.* Van Duyse refers to a hyaline degeneration of the cell protoplasm seen in sections stained with Van Gieson and most obvious in transverse sections. He gives no reason for his assertion that hyaline degeneration was present. He also comments on the contrast between the yellow colour of the tumour fibrils which assimilate the picric acid of the van Gieson and the red of the connective tissue nearby, stained with fuchsin.

SUMMARY

A further case of leiomyoma of the iris is described. The clinical history and appearance vary greatly. Those of van Duyse, Verhoeff and Ellett had a history of twenty years' duration, that of Kahler *et al.* two, and of Frost only one. At

the time of operation the patient of van Duyse was twenty-eight, of Verhoeff thirty-three, of Frost forty-six, of Ellett forty-seven, and of Kahler *et al.* forty-six. In each case the tumour was on the lower part of the iris, one in the lower nasal quadrant, one in the middle, and four (including the above) in the lower temporal quadrant. In the case reported by Verhoeff the tumour was suspended from the anterior surface of the iris by a narrow pedicle. The remainder presented as sessile tumours which appeared to originate from the depths of the iris. All were vascular, and several were prone to recurrent haemorrhage. van Duyse records that his patient had nine hyphaemas before iridectomy was performed. The only record of cataract is in the present case.

The site of the tumour calls for comment. Although the number of cases is too small to allow sure conclusions, it is remarkable that all were situated in the lower half of the iris. This would suggest that the tumours had arisen near the foetal fissure, and that their origin may be traced to a defect arising at the time of its closure. Verhoeff states that in his case the tumour was "nowhere connected with the iris muscles or pigment epithelium" and that it seemed likely "that it originated from stroma cells of the embryonic uvea, possibly from misplaced cells which ordinarily would have taken part in the formation of the ciliary muscle." The situation of the tumour in all cases reported adds some weight to his suggestion.

ACKNOWLEDGMENTS

I wish to thank Dr. Andrew Brenan, Director of the Pathological Laboratory at St. Vincent's Hospital, Melbourne, for affording me the facilities to investigate this case, Miss Thornton for preparing the sections, and Mr. E. Matthei, Director of the Faculty Workshops at the University of Melbourne, who prepared the photo-micrographs.

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RECESSION OF THE INFERIOR OBLIQUE*

BY

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Introduction. Vertical imbalance of the eyes related to abnormalities of the inferior oblique is receiving ever-increasing attention, and the accumulation of the results of surgical intervention for the cure of the condition already enables an opinion to be offered as to the effectivity of such treatment.

Overaction of the inferior oblique has interested surgeons for many years, and in certain types of case its cause is still in doubt. Particularly is this so in its relationship to the horizontal squints in children. Doubtless many cases of overaction are due to a paresis of a superior oblique or a superior rectus, but there still remain a number which cannot be explained so readily. The writer tends to the belief that the latter are partly due to a compensatory overaction of the inferior oblique in an endeavour to abduct the eye to counteract excessive convergence by the internal rectus, and probably linked up with a low-grade masked paresis of the external rectus.

It has been the custom to correct the horizontal element in a squint and so far as possible allow the vertical component to right itself, perhaps with the aid of orthoptic exercises. That this procedure is incorrect receives confirmation from many authorities including Spaeth, Gibson, Wheeler, Guibor, Dunnington, Hughes, Wagman, Prangen, Foster and Anderson. Anderson[1] found that 53 per cent. of convergent squints in children were associated with a vertical defect and that 30 per cent. were characterised by overaction of the inferior oblique. The writer reviewed the last 100 cases in his own clinic which required operation for a horizontal defect of convergent type and found that 48 of them had a vertical defect in addition, which was sufficiently marked as to require operative correction.

It therefore appears to be essential that greater attention should be devoted to the vertical element in the convergent squints. Apart from the cosmetic improvement, which is often considerable, the writer is convinced that in correcting the vertical defect a better functional result is obtained, as the tendency to hyperphoria is eradicated.

Operations on the inferior oblique are not by any means a new thing, but it is only in comparatively recent years that a rational

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approach to the problem coupled with adequate investigation have led to more reliable results being obtained. Wheeler,[2] Wagman,[3] Berens, Conrad and Loutfallah[4] have resected the inferior oblique in cases of paresis of this muscle. White,[5] Guibor,[6] and Prangen[7] have recessed the muscle to correct its overaction.

Tenotomy to reduce overaction of the inferior oblique has been practised for over a hundred years, but the operation has only been used scientifically during the last twenty to thirty years, mainly as a result of improvements in anaesthesia and surgical technique. The transconjunctival route for the operation of tenotomy of the inferior oblique is linked with the name of Guibor, but Landolt described it in 1885.[11] Banister[12] condemned the operation of tenotomy, and it must be conceded that it is only applicable in extreme cases of overaction of the muscle, and that no grading of the result can be obtained. The writer would also add that it deprives the eye of the torsion effect of the muscle. Duane tried a partial tenotomy of the muscle, but was not impressed with the results. The writer has performed this operation on several occasions, and finds that the results are unreliable.

White stated that the indications for reducing the overaction of the inferior oblique were :—

(1) To correct a secondary overaction of the inferior oblique caused by a paresis of the superior rectus of the fellow eye.

(2) To correct a secondary contracture due to a paralysis of the superior oblique of the same eye.

The writer would like to add a further indication, *viz.*, overaction of the inferior oblique associated with a horizontal squint, especially convergent in type, and not always definitely due to paresis of a vertically acting muscle.

In consequence of the unreliability of partial tenotomy of the muscle, and the fact that a full tenotomy could not produce a graded result, attempts were made to recess the muscle. This operation has now been performed by several surgeons, but the number of cases reported is still comparatively small. Despite this the results are so far encouraging. White, Guibor and Prangen have described the technical details of the operation, but do not offer many case-reports.

TECHNIQUE

The surgical approach to the inferior oblique may be either through the lower lid, or by the transconjunctival route. For recession of the muscle the latter method is preferable, as it gives a much better access to the insertion of the muscle, and enables a resection or advancement of the external rectus to be carried out at the

same time, as is so often required. Both Landolt and Guibor favour this approach.

Guibor and White recessed the inferior oblique in such a way as to bring the new insertion further forwards and to some extent downwards, *i.e.*, a true recession as the insertion is made to approximate to the origin. Prangen[7] placed the new insertion 6 to 7 mm. behind the insertion of the external rectus and on the same horizontal line with the latter.

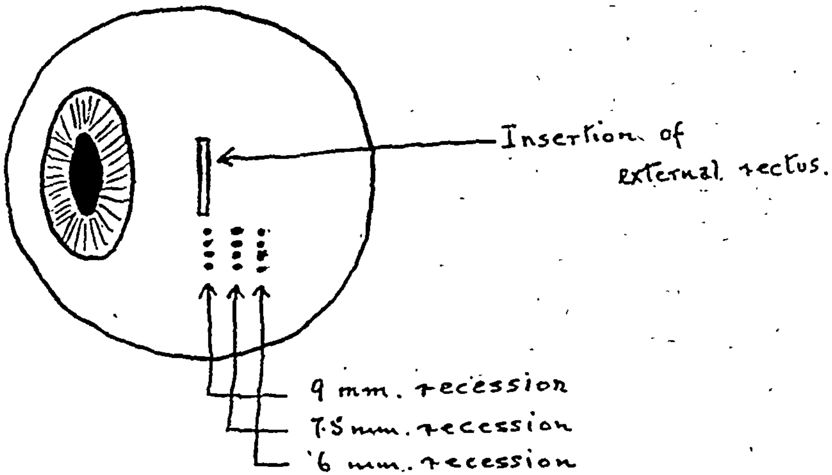
The writer attempted a series of recessions adopting the technique of Prangen, Guibor and White, but found that the effect was very variable and often almost negligible. In consequence the modification described below is suggested. The results of some of the earlier cases were not entirely satisfactory, and this was found to be due to under-correction, *i.e.*, insufficient recession. In the later cases the increased recession proved adequate to correct the defect.

In the main the operation suggested is that of Prangen and Guibor, the transconjunctival route is used, and the eye is rotated upwards and inwards, and maintained in that position by a silk traction suture inserted through the bulbar conjunctiva near the outer limbus. It appears to be essential to free the muscles from Tenon's capsule in order to give an uninterrupted view of the field of operation and prevent confusing post-operative adhesions. If operation is also required on the external rectus this is detached and allowed to recede into the wound, being retained by sutures. Otherwise it is held upwards out of the way by a squint hook or retractor.

The inferior oblique muscle is then located by Guibor's method with a squint hook, and the value of freeing Tenon's capsule fully is then appreciated, as there is less tissue to cause confusion. When the oblique has been lifted up into the wound it is cleared of all extraneous tissue, and the check ligament attaching it to the external rectus is divided. The muscle is then followed up to its insertion, which should be identified with certainty, and a muscle clamp, *e.g.*, Prince's forceps, applied to the tendon close to the insertion in the sclera. Then tendon is then divided. Two catgut sutures are passed through the end of the muscle, one at each corner, and secured with a " whip stitch," and the muscle clamp removed. The sutures are then passed through the superficial layer of the sclera and each one tied separately, so that the muscle is anchored in position. The suturing to the sclera is done in such a way that the knots are one above the other, causing the end of the muscle to be spread out flat with its edge vertical. This seems to give a neater result than the single stitch of Prangen. The conjunctiva is closed, after reattaching the external rectus in

the appropriate cases, using a continuous silk suture. This type of suturing is quite adequate, and renders its removal very much easier, especially in children, than interrupted sutures.

The position on the sclera to which the muscle is attached is further forward than that suggested by Guibor and Prangen. The amount of recession required depends on the pre-operative investigation and measurements. For a full recession the writer has placed the new insertion of the muscle immediately inferior to the insertion of the external rectus, but for lesser effects the muscle may be inserted at varying distances behind this point, but not more than 4 mm., as beyond this the recession appears to be inadequate and unreliable. The line of recession for a graded result is posterior to that for a full recession, and is kept horizontally just below the lower border of the external rectus.



To illustrate the positions for insertion of the left inferior oblique.

It will be seen therefore that, in spite of what Guibor and Prangen advocate, the external rectus need not be detached in order to recess the inferior oblique.

SUMMARY

A review of the operative treatment for overaction of the inferior oblique is presented, and some of the disadvantages of present methods are discussed.

Indications for operation on the inferior oblique are given, particularly in cases of overaction of the muscle.

It is suggested that recession of the muscle is a practicable procedure, and is preferable to partial or complete tenotomy.

CASES OF RECESSION OF INFERIOR OBLIQUE

No.	Age	Type of squint	Operation	Result
1	14	Conv. concom. squint 35° L.E., overaction L.I.O.	L.E.: 5 mm. recess. int. rect. 10 mm. resect. ext. rect. 9 mm. recess. inf. oblique.	Angle of squint ÷ 5° overaction of inf. oblique corrected.
2	5	Conv. concom. squint 25° L.E., overaction L.I.O.	L E.: 5 mm. recess. int. rect. 8 mm. resect. ext. rect. 6 mm. recess. inf. oblique.	Angle of squint 0° overaction of inf. oblique corrected.
3	5	Conv. concom. squint 30° L.E., overaction L.I.O.	L.E.: 5 mm recess. int. rect. 10 mm. resect. ext. rect. 9 mm. recess. inf oblique.	Angle of squint ÷ 5° overaction of oblique corrected.
4	8	Conv. concom. squint 35° L E., L/R 7, bilateral overaction I.O.	L.E.: 5 mm. recess. int. rect. 10 mm. resect. ext. rect 8 mm recess. inf. oblique.	Angle of squint 0° L/R 2. No overaction L.I.O. R.I.O. still overacting.
5	7	Conv. concom. squint 35° R.E., overaction R.I.O.	R E.: 5 mm. recess. int. rect. 10 mm resect. ext rect. 6 mm. recess. inf. oblique.	Angle of squint ÷ 5° overaction of R.I.O. corrected.
6	8	Conv. concom. squint 25° R.E., R/L 5., overaction R.I.O.	R.E: 5 mm. recess. int. rectus. 10 mm. resect. ext. rectus. 8 mm. recess. inf. oblique	Angle of squint ÷ 5° overaction of inf. oblique corrected.
7	14	Conv. concom. squint 35° R.E., R/L 15., overaction R.I O.	R.E.: 5 mm. recess int. rectus. 10 mm. resect. ext. rect. 6 mm. recess. inf. oblique.	Angle of squint ÷ 5° R/L 5. Overaction of inf. oblique corrected.
8	41	R/L8., overaction R I.O. paresis R.S.O.	R.E.: 7 mm. recess. inf. oblique.	R/L 0° overaction of inf. oblique corrected.
9	5	Overaction L.I.O. paresis L.S.O.	L.E.: 9 mm. recess. inf. oblique.	Angle of squint 0° overaction of inf. oblique corrected.
10	6	Conv. concom. squint 25° L.E., L/R 7., overaction L.I.O.	L E. 5 mm. recess int. rect 10 mm resect. ext. rect. 9 mm. recess. inf. oblique.	Angle of squint ÷ 5° L/R 0° overaction of inf. oblique corrected
11	7	Conv. concom. squint 5° bilateral overaction of inf obliques.	R.E.. 8 mm resect. ext. rectus. 9 mm. recess. inf. oblique. L.E.: 9 mm recess. inf. oblique.	Angle of squint 0° 0·0 No overaction of inf obliques.
12	7	Conv. concom. squint 30° R.E., overaction of inf. oblique.	R E: 5 mm. recession int. rectus. 10 mm. resection ext. rectus. 8 mm. recess. inf. oblique.	Angle of squint — 3° no overaction of inf oblique.

Evidence is produced that the position for the new insertion of the inferior oblique is important, and that the positions already described for recession of the muscle do not give reliable and accurate results.

The results of cases are given.

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STATISTICAL DATA OF MY CATARACT OPERATIONS PERFORMED WITH A NEW SUTURE OF THE SCLERA

BY

F. PAPOLCZY

BUDAPEST

WHEN studying the history of cataract operations we can see that this most important and most frequent of eye operations has undergone very great changes since the first operations, performed almost 2,000 years ago, up to now. This process, however, was not made equally, but in periods of progress more or less defined by certain great medical discoveries.

The oldest cataract operations which quacks performed during many centuries were depressions or reclinations. They were carried out by inserting a pointed, awl-like needle through the sclera into the eye, and pushing the opaque lens backwards or downwards into the vitreous body. As a consequence of this operation at least 60 per cent. of the patients lost their sight after a longer or shorter time owing to infection, haemorrhage into the vitreous and glaucoma. It often happened that sooner or later, after surgical intervention, the cataract either returned to its original place, or luxation into the anterior chamber took place.

In the middle of the eighteenth century Daviel found out that

much better results could be obtained by removing the cataract through a corneal wound. But after this operation, in 15-20 per cent. of the cases, another complication arose: suppuration of the wound, in consequence of which the eye was often lost.

The perfecting of operative methods, in the present meaning of the word, became possible only when, in the earlier part of the nineteenth century, Davy, Wells, Jackson and others discovered narcosis, and in the latter part of the nineteenth century, local anaesthesia was discovered by Koller and Schleich. Almost simultaneously, Lister found out, on the basis of the research work of Pasteur, that infection caused suppuration of the wound, and that sterilisation and asepsis were the only means of protection against it.

Under these favourable conditions Snellen's cataract operations performed with a conjunctival flap after careful pre-operative treatment were a great advance at the end of the nineteenth century.,

At that time everywhere complete iridectomy and extra-capsular operations were done by making a large incision above the iris and then removing the nucleus and cortex as far as possible with a spoon. When, however, part of the capsule and a great part of the cortex remained, inflammation of the operated eye ensued, and it often demanded weeks of treatment. Frequently a dense secondary cataract developed. It was observed that if the capsule forceps was blunt, or the capsule was very thick and resistant, the cataract could be removed together with the capsule. In this case there is no danger of inflammation or after-cataract.

After this experience, Török, Elschnig and Stanculeanu, at the beginning of the twentieth century, devised forceps with which in a great number of cases the cataract could be removed entirely, that is to say with the capsule. Not long afterwards it was found that even better results could be obtained by performing not an entire, but a basal iridectomy, thus leaving the pupil untouched. This led to the round pupil intra-capsular extraction.

The round pupil operation has, however, the disadvantage that in case of rupture of the wound prolapse of a greater or smaller part of the iris can occur, or this may be wedged in the wound. In 1867 Williams found that this complication with its unpleasant and sometimes tragic consequences could be avoided by suturing the wound. The first successful suture was described by Mendoza in 1889. Liégard, in 1913, published a new method which, with a few smaller modifications, still proves useful. Later Kuhnt's conjunctival flap employed by Blaskovics, and Elschnig's, Horváth's and lately McLean's sutures were the most successful and most frequently used.

By using the above-mentioned and many other similar sutures the danger of prolapse of the iris or the iris getting wedged in the wound was considerably diminished, but not completely eliminated. Experience shows that these sutures may bring about certain disturbances or even serious complications regarding the healing of the wound; so naturally ophthalmologists endeavoured to find newer methods which would yield still better results.

The requirements of a suture which is to close the cataract wound well and to ensure its undisturbed healing are :—

1. The suture should not be inserted directly into the corneo-scleral wound, because suppuration of the suture may cause infiltration of the cornea, and wound infection. But it should not be inserted too far from the wound either, because then it is impossible to avoid rupture of the wound with all its consequences.
2. It must unite the edges of the wound exactly in their original place lest gross astigmatism arise.
3. The conjunctival flap must be large enough to cover the wound entirely.

The insertion of the suture should not complicate or unduly prolong the operation, lest ophthalmic surgeons of limited experience should be unable to perform it.

Bearing in mind these considerations and requirements I have now been using for years a new suture for my cataract operations, the original idea of which was given to me by Imre's method. In cases of complicated cataract he made a semi-circular flap into the bulbar conjunctiva, and severing it as far as the limbus turned it back upon the cornea. At 12 o'clock, about 2 mm. from the limbus, he inserted a thread horizontally in the superficial layers of the sclera, then inserted the same thread in that part of the conjunctival flap which was originally above these points. Then pulling the thread out of the wound, he formed a loop. The cataract incision was made in the usual way with Graefe's knife. After extraction the conjunctival flap was replaced upon the sclera, smoothed down, and then the thread was knotted twice.

This method has the disadvantage that, as the detached conjunctiva is elastic and shrinks, it is impossible to insert the suture exactly at the corresponding places in the sclera and the conjunctiva. In consequence the edges of the wound cannot be fixed exactly in their original position. Another disadvantage is that it is very difficult to make the cataract incision after having made and turned back the conjunctival flap previously.

I endeavoured to eliminate these difficulties by inserting the thread through the conjunctiva into the superficial layers of the sclera, and making the incision and the conjunctival flap afterwards. Thus my method is the opposite of Imre's operation.

The following is a detailed description of my operation. After the usual preparation I open the palpebral fissure with Oláh's speculum. The use of this and other similar instruments is of great advantage in intra-ocular operations, because the assistant need not trouble to retract the lids during the whole of the operation.

I fix the eye from above by a suture inserted in the superior rectus, from below by fixation forceps next to the limbus. Then I insert a 6·0 black nylon suture at 12 o'clock, 1 mm. from the limbus, parallel to it through the conjunctiva into the superficial layers of the sclera (Fig. 1). After this I proceed to make the cataract incision with Graefe's knife. But when the corneal part of the incision has been made, and the knife, still under the conjunctiva, has reached the level of the suture, I do not continue the incision, but carefully withdraw the knife from the wound (Fig. 2). Then, above, I make a semi-circular conjunctival flap with scissors, and detaching it from the sclera to the thread, turn it back on the cornea (Fig. 3). After drawing out both threads through the conjunctival tissue with anatomical forceps, I form a loop and cut through the shreds of tissue around the wound with scissors (Fig. 4).

Then after making a basal excision in the iris above, I grasp the capsule from below with Arruga's forceps, and if it is very tense, I use Imre's or Blaskovics' forceps. Afterwards I draw the lens slowly outwards with lateral movements. I expel it by exerting

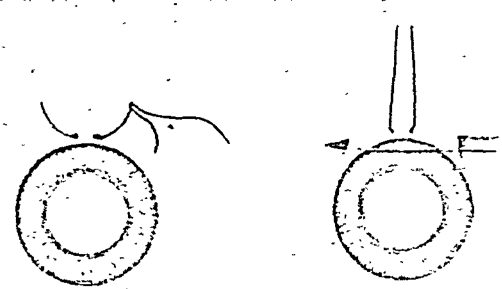

FIG. 1. FIG. 2.

FIG. 1. Insertion of the needle through the conjunctiva into the sclera.
FIG. 2. Making the corneo-scleral incision with Graefe's knife.

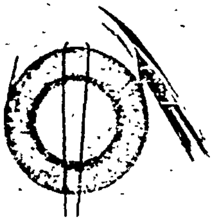

FIG. 3.

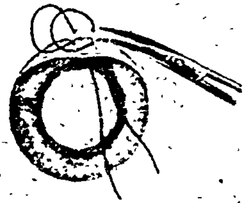

FIG. 4.

FIG. 3. Making a conjunctival flap with scissors. FIG. 4. The cuttir of the subconjunctival tissue, which keeps the wound together.

slight pressure upon the cornea at the lower limbus i.. .... opposite direction with Imre's ring-instrument. I endeavour to remove the cataract by tumbling. If this proves impossible, as for instance with large, flat, hard cataracts, or with a narrow pupil, the assistant lifts the iris slightly off the lens from above with a cyclodialysis spatula or with the finer hook of Horvath's zonulo-ruptor, so that its edge will fit into the pupil. I do not lose hold of the capsule during the extraction. With tumescent or liquefied cataracts, when it is impossible to grasp the capsule, I make a small horizontal incision as recommended by Csillag with a keratome, and subsequently remove the capsule after the extraction: this usually succeeds. After the removal of the cataract I replace the conjunctival flap, smooth it out, knot the thread three times, and replace the iris with a cyclodialysis spatula.

Should rupture of the capsule occur, I remove the remnants of the cortex with a spoon, and finally irrigate the anterior chamber and remove the remnants of the capsule with capsule forceps. I seldom have to make a complete iridectomy after extra-capsular operations.

I cover the operated eye with small squares of gauze, loose cotton-wool and Snellen's perforated aluminium cup, held in place with two straps of adhesive plaster fixed to the forehead and cheek. Both eyes are bandaged and the patient is put to bed for the first day. I change the dressing after 24 hours, and later once a day. The patient may sit up in an arm-chair on the second day. I remove the sutures on the tenth day. Until then the operated eye is kept bandaged.

In the years 1941-1946 I performed 325 senile cataract operations, employing my suture. At first I was not very sure of its success, but after much experience, I have found that this suture has a very favourable influence upon the healing of the wound.

On account of the prevailing opinions, I performed operations with a round pupil only rarely in the beginning, but more and more frequently later on. During the first two years, *e.g.*, in cases of exophthalmos, tumescent cataract, or when the pupil could not be dilated widely enough, or when the other eye had already been operated in this way, and also in cases of extra-capsular operations I made a complete coloboma. The first table shows the results of my operations in 1941-42.

Table I

152 operations performed in 1941-1942

INTRA-CAPSULAR		EXTRA-CAPSULAR	
Round pupil	Coloboma	Round pupil	Coloboma
68 = 44.7 %	45 = 28.6 %	15 = 10.0 %	24 = 15.7 %
113 = 74.3 %		39 = 25.7 %	

Of these WITH ROUND PUPIL: 44.7 % + 10.0 % = 54.7 %
Of these WITH COLOBOMA : 29.6 % + 15.7 % = 45.3 %

During this time I performed 54·7 per cent. operations with a round pupil and 45·3 per cent. with an iridectomy: 74·3 per cent. were intra-capsular, 25·7 per cent. were extra-capsular operations. At that time I was not yet satisfied with the results of my operations. But later I acquired more practice with this method, and I also found out that the generally accepted opinions regarding operations with a round pupil were out of date. I saw that they could be performed much more frequently without the least danger, even as routine operations. In the following years I made a coloboma only in cases of complicated cataract, prolapse of the vitreous body, or unintentionally, as, for instance, in the case of a markedly tumescent cataract, or if escape of the aqueous floated the iris before the knife. The second table shows the results of my operations performed in 1943-46.

TABLE II

173 operations performed in 1943-1946

INTRA-CAPSULAR		EXTRA-CAPSULAR	
Round pupil	Coloboma	Round pupil	Coloboma
136 = 78.6 %	11 = 6.3 %	22 = 12.7 %	4 = 2.4 %
147 = 84.9 %		26 = 15.1 %	

Of these WITH ROUND PUPIL : 78.6 % + 12.7 % = 91.3 %
Of these WITH COLOBOMA : 6.3 % + 2.4 % = 8.7 %

During this time I performed 91·3 per cent. operations with a round pupil and only 8·7 per cent. with iridectomy; 84·9 per cent. were intra-capsular, 15·1 per cent. were extra-capsular operations.

My statistics prove that with the help of these sutures I endeavoured always to use the intra-capsular method, and from 1943-1946 with a round pupil; the combination was nearly always successful. In view of these favourable possibilities the indications regarding operation will have to be altered. Nowadays it is not necessary to wait for the cataract to be completely "mature." The operation should be performed as soon as the patient's vision has deteriorated to such a degree that he is unable to carry on his work, or becomes a burden to his family and himself. In many cases I operate for cataract when vision is 5/15 or 5/10 when the patient is a person whose occupation demands good eye-sight, such as mechanics, printers and chauffeurs, etc. When there is cataract in both eyes, I operate first on one eye and only 10-12 days later on the other. Operation can be performed on both eyes then at the same time without the slightest risk or difficulty, but I have found that having both eyes bandaged for several days had a very bad effect on the patients.

The use of my suture makes the operation longer, and for this reason many surgeons are against it. But it is not to the detriment of the patient, and therefore we may not grudge these few minutes if by taking a little longer to operate we are able to improve the results substantially.

The most dangerous complications which may arise during or after cataract operations are loss of vitreous, expulsive

haemorrhage, infection, rupture of the wound, prolapse of the iris, and finally secondary glaucoma. In the older statistics of operations these complications appeared in a considerable number of cases, but nowadays they are much rarer owing to careful pre-operative treatment, to asepsis, to the development of operative technique and to correct post-operative treatment.

The third table shows the complications of the cataract operations which I performed in the years 1941-1946.

TABLE III

Number of operations	325	
Loss of vitreous	3	= 0.9 %
Expulsive haemorrhage	0	—
Infection	0	—
Haemorrhage into the a.c	45	= 13.8 %
Prolapse of the iris	4	= 1.2 %
Glaucoma	1	= 0.3 %

Thus loss of vitreous occurred in 3 cases (0·9 per cent.). With one patient who was highly myopic, liquefied vitreous prolapsed from the anterior chamber when the section was made. In another case, also that of a highly myopic patient, the zonular fibres were extremely weak, and in consequence the lens slipped into the vitreous when the capsule was grasped. In both cases the cataract was removed with Weber's loop. In the third case the patient was very nervous, the palpebral fissure was exceptionally narrow and could not be widened by canthotomy. In these three cases I made a complete iridectomy.

I had no case of expulsive haemorrhage or infection. After careful pre-operative treatment these complications do not arise nowadays.

Haemorrhage into the anterior chamber occurred in 45 cases (13·8 per cent.), usually 3-6 days after the operation. The cause was either spontaneous haemorrhage or rupture of the wound. At first I was very perturbed by rupture of the wound when performing operations with a round pupil, but later I saw, to my great surprise, that even in cases when the anterior chamber was entirely filled with blood, no prolapse of the iris occurred. In one case the iris was wedged in the wound: it could be freed from the cicatrix a few weeks later by cyclodialysis. In connection with rupture of the wound the pupil was distorted in four cases (1·2 per cent.).

As the above-mentioned data show, my suture does not prevent rupture of the wound, but it considerably decreases and limits the possibility of the opening of the wound, so that the aqueous of the anterior chamber cannot escape with such force as to carry the iris with it.

Prolapse of the iris or its milder form, wedging of the iris in the wound, may occur a few hours after a cataract operation with round pupil performed with this suture.

Immediately after the operation, or a few hours later, when the edges of the wound are not yet glued together, the iris may slip out of the wound if the eyelids are pressed together. This happened in 4 cases (1·2 per cent.) of my cataract operations. I had this unpleasant surprise when changing the bandage for the first time, 24 hours after the operation. After anaesthesia with pantocain and careful opening of the wound I could replace the iris with a cyclodialysis spatula in two of the cases, but in the other two cases, the lips of the wound were already glued together so firmly that I could only excise the prolapsed part of the iris with forceps and scissors.

On account of this experience I think it would be better to change the bandage for the first time in the afternoon of the day of the operation, because then the wound is not yet firmly closed, and it is easy to replace the prolapsed knuckle of the iris.

Apart from rupture of the wound, distortion of the iris occurred in another 6 cases (1·8 per cent.), probably as a consequence of the eyelids having been strongly pressed together in the hours following the operation, as in the case of prolapse of the iris, or because of inefficient reposition. It is of no importance, and can be considered merely as a minor cosmetic disadvantage.

Secondary glaucoma occurred in 0·3 per cent. After an intracapsular cataract operation with a round pupil a widespread detachment of the choroid occurred, but three weeks later it was attached again. Six weeks after the operation the tension had increased to 60 mm. Hg. Pilocarpine was ineffective, so an iridectomy had to be performed. After this the tension decreased for some time, but six months later it was again 56 mm. Hg, so I decided to perform a cyclodialysis, which permanently reduced the tension. No case of secondary glaucoma occurred in consequence of iris prolapse, impacted iris, or displacement of the pupil, as might have been expected.

Among other less important complications I saw detachment of the choroid in 5 cases, but this always disappeared after a while. I never observed detachment of the retina.

After extra-capsular operations and rupture of the wound a slight irritation of the iris sometimes developed, but with mydriatics and warm compresses it was possible to quieten the eye so that other treatment proved unnecessary.

From all this we can see that the round pupil cataract operations performed with adequate sutures yield much better results than the older "flap method" carried out with a complete iridectomy and

without sutures. The operation with a round pupil is quite free from danger when performed according to my method. I wish to emphasise that this operation may be done even in cases upon which we would not have dared to operate formerly.

This is proved by the fact that among the operations mentioned in my statistics there were 25 cases of patients with impaired hearing, 4 cases of stone-deafness, 6 cases of high myopia, 1 case of advanced Graves' disease, 2 patients suffering from emphysema and severe attacks of dyspnoea, 2 cases of nystagmus—even during the operation—2 cases of deaf and dumb persons, 1 epileptic patient and one with senile tremor of the head. In all these cases I performed successful operations with round pupils, and the state of the patients had not the slightest influence either upon the operation or upon the healing of the wound.

I must mention, however, that operations with a round pupil should be performed by skilful and experienced eye surgeons only. Beginners should practice the flap operation with a complete iridectomy and perform this technically more difficult operation only after considerable experience.

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THE ILLUMINATION OF THE SNELLEN CHART*

BY

M. GILBERT *and* R. G. HOPKINSON

THE problem of adequate lighting in schools, homes, offices and buildings in general has given rise to a study of the effect of illumination and contrast on visual performance. The programme of work has been carried out in close collaboration with Mr. H. C. Weston, of the Medical Research Council, to whom the authors' thanks for the benefit of valuable discussions are due, and under the aegis of the Joint Committee on Lighting and Vision of the Building Research Board and the Medical Research Council.

It was thought that clinicians would be interested in particular in the effect of illumination level on the visual acuity of observers as assessed by the standard Snellen chart.

The subjects of the experiment were 15 adults from the staff of the Building Research Station, in the age group 20-40. They

TABLE 1—*Classification of Subjects Employed on Visual Acuity Tests*

GROUP 1—*Subjects with Normal Acuity*

Subject	Binocular Acuity on Snellen Chart at 30 f.c. (M.R.C.)	Refraction	R.E.	L.E.
1. A.B.	6/4.5	Emmetrope.	—	—
2. C.M.P.	6/4.5	Myope, corrected.	—2.0	—2.75
3. *H.M.	6/4.5	Hypermetrope, corrected.	+4.5, —0.5 ax. 30°	+4.5, —0.5 ax. 130°
4. W.H.W.	6/4.5	Uncorrected.	+0.25, —0.75 ax. 180°	+0.25, —0.75 ax. 160°
5. *M.G.	6/4.5	Myope, corrected.	—3.25, —1.75 ax. 180°	—2.75, —2.5 ax. 180°
6 *C.P.	6/6	Astigmat, corrected	—1.0 ax. 155°	—1.5, ax. 20°
7. *E.S.J.S.	6/6	Hypermetrope, corrected.	+4.0, —0.5 ax. 180°	+3.75, —0.5 ax. 180°
3. *H.M.	6/6	Hypermetrope, uncorrected.	*see* 3	above
8. *P.M.	6/6	Hypermetrope, corrected.	+3.0	+3.0, —1.0 ax. 120°
6. *C.P.	6/7.5	Astigmat, uncorrected.	*see* 6	above
		GROUP 2—*Subjects with Moderate Acuity*		
9 W.E.S.	6/9	Myope, uncorrected.	—0.75, —0.5 ax. 180°	—0.5
10 G.M.	6/9	Astigmat, uncorrected.	—1.75 ax. 5°	+0.5, —1.75 ax. 175°
5. *M.G.	6/12	Myope, partial correction.	Full cyl. correct partial sph. corre	ion, (*see* 5 above) ction (—1.0 sph.)
11. G.B.	6/18	Astigmat, uncorrected.	—2.5 ax. 90°	—2.5 ax. 95°
12. H.My	6/24	Myope, uncorrected.	—1.75	—2.0
13. *M.L.	6/24	Myope, partial correction (for full correction *see* 13 below).	—2.75, —1.0 ax. 90°	—3.5, —1.25 ax. 95°
14. J.F.	6/36	Hypermetrope, uncorrected.	+1.75, —0.25 ax. 180°	+1.5, —0.5 ax. 65°
15. J.P.	6/36	Myope, uncorrected.	—2.0, —1.0 ax. 180°	—1.0, —1.0 ax. 160°
		GROUP 3—*Subjects with Poor Acuity*		
8. *P.M.	6/36	Hypermetrope, uncorrected.	*see* 8	above
7. *E.S.J.S.	6/60	Hypermetrope, uncorrected.	*see* 7	above
5. *M.G.	6/60	Myope, uncorrected.	*see* 5	above
2. *C.M.P.	6/60	Myope, uncorrected.	*see* 2	above
13. *M.L.	6/60	Myope, uncorrected.	—4.5, —0.75 ax. 120°	—5.5, —0.5 ax. 110°

* Subjects marked thus made observations with and without their correction.

varied from emmetropes of 6/4·5 vision to ametropes of 6/60 vision. Various refractive errors were included in the sample. Some of the observers who habitually wore a correction made observations with and without their correction, and in addition two subjects (both myopes) made observations with a partial correction with which they were familiar. Table I summarises the refractive defects of these observers, which were measured by Mr. J. L. H. Moss, of the Medical Research Council, who also assessed the visual acuity on a Snellen Chart illuminated to 30 ft. candles by fluorescent ("daylight") lamps.

For the observations, the subject sat 6 metres from a white wall on which the Snellen chart was displayed. The whole wall as well as the chart itself was illuminated by screened incandescent light sources. Additional room lighting produced a brightness of the surroundings of the same order as, but lower than, the brightness of the chart.

After an initial period of adaptation, the observer was asked to read the letters on the Snellen chart with an illumination of only 0·1 ft. candles. When he had read as far as possible, the illumination was slowly raised to 3 ft. candles (a change of 30 : 1) and the chart was again read as far as possible. Finally the illumination was raised to 100 ft. candles (a further change of approximately 30 : 1). It was felt that familiarity would not influence the reading of the chart at the higher levels of illumination, since the smaller letters became visible only at these higher levels, and were not recognised at the lower levels. There was in addition a considerable time interval between the successive showings of the chart, so that it was unlikely that the subject would retain any clear memory of the chart, as a number of other charts (with different contrasts, etc.) were also read at each level of illumination. It should also be mentioned that a magnified chart was produced photographically to enable a complete line of letters of the 6/60, 6/36 and 6/24 size to be available for those subjects with poor vision.

The results obtained were plotted in the form of a relationship between illumination (log. scale) on the chart, and line acuity (inverse log. scale of angular subtense of critical detail) for each of the 15 subjects. The subjects were then grouped in accordance with the Snellen acuities measured by the refractionist, and the observations in each group were averaged. The purpose of this grouping was to show whether the effect of illumination on acuity was the same or different for observers with normal or with subnormal vision.

The results are shown on Figs. 1A and 1B. It can be seen from the averaged curves that an increase in illumination of the

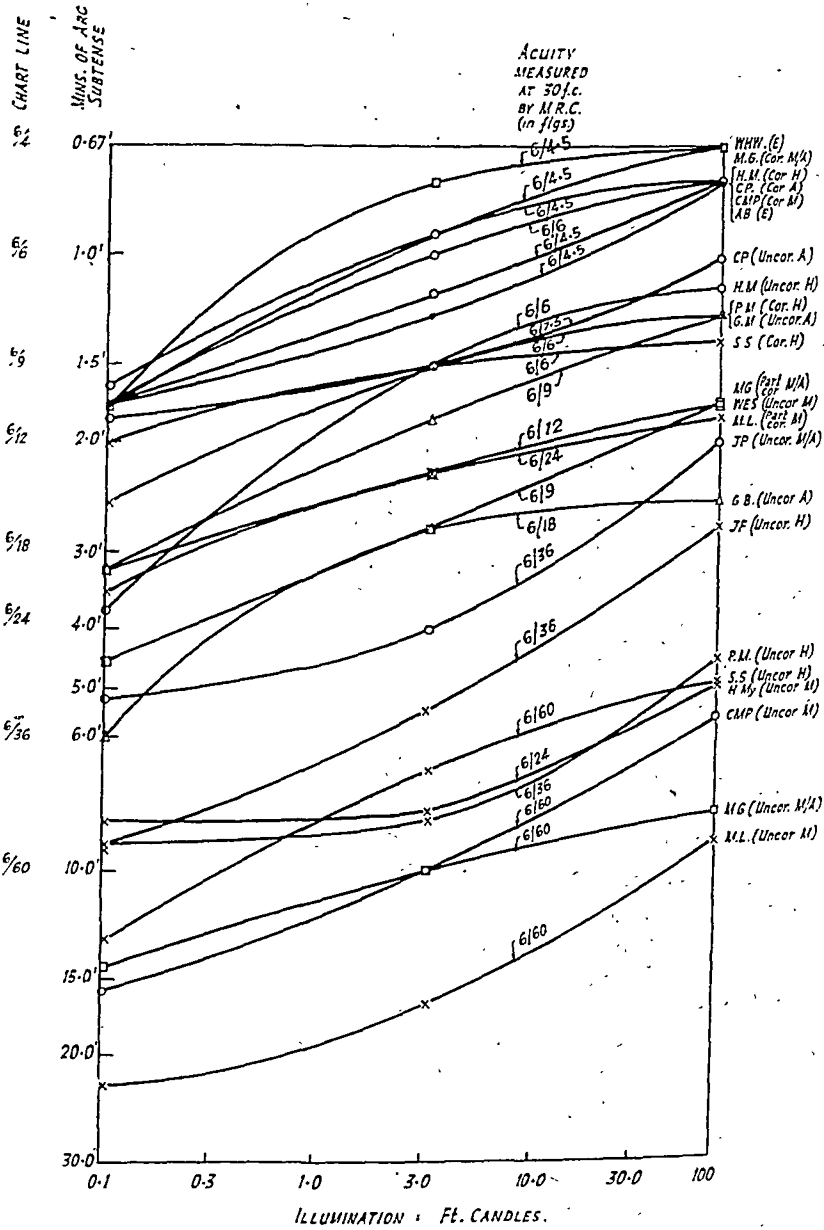

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FIG. 1A. ILLUMINATION v ACUITY FOR STANDARD SNELLEN CHART.

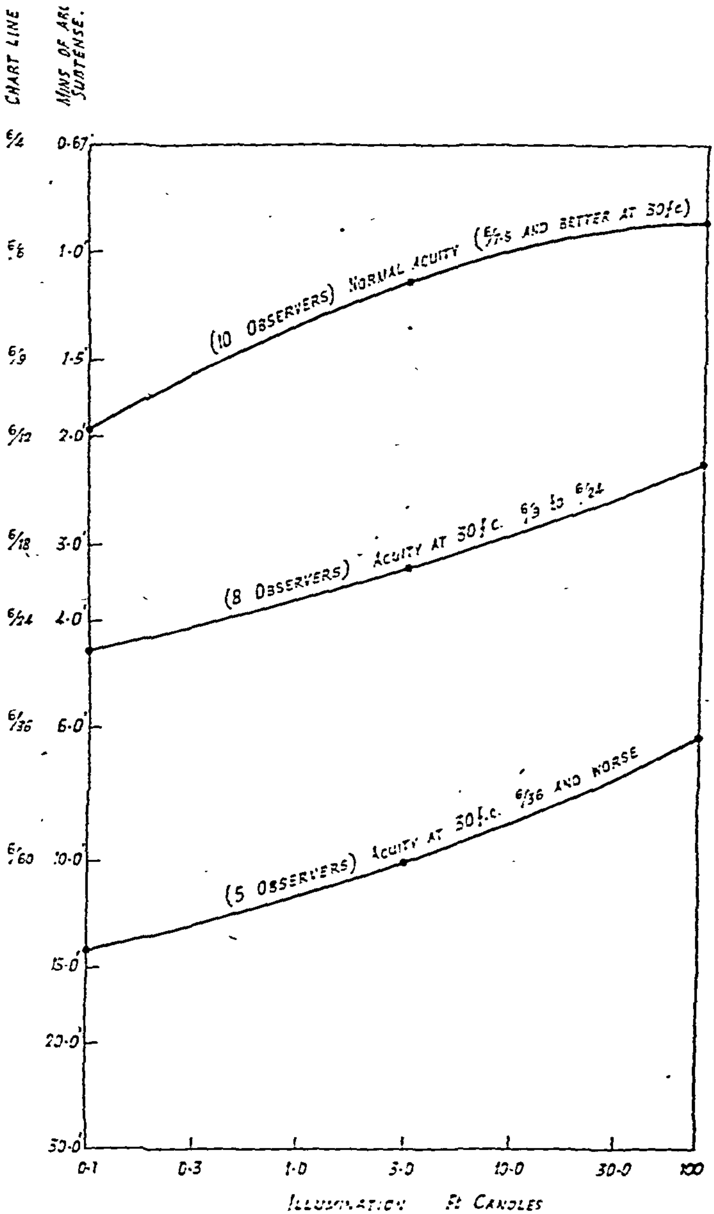

FIG. 15. ILLUMINATION v ACUITY FOR STANDARD SNELLEN CHART
(AVERAGES FOR OBSERVERS WITH SIMILAR ACUITIES)

order of 10:1 improves the acuity by one line on the Snellen chart. The effect is rather less for observers with good vision than for those with poor vision, especially for high levels of illumination. However, the result is probably a useful working rule. There were some deviations from the general rule by some subjects, which are not shown by the averaged curves, but there is evidence that the errors were probably experimental and not systematic.

The data would suggest that it is necessary to set some standard of illumination of the Snellen chart, especially when this is used as a pass test of visual acuity for entrants to a trade or profession. The investigation was not, of course, concerned with the optimum level of illumination for clinical practice, although it would be of interest to know the range of illumination levels within which clinicians would normally work. A survey of clinical practice was made in 1928 in the U.S.A.,* but no recent surveys appear to have been made in this country. It is realised that for visual examinations conducted under unfavourable conditions of working, the clinician often finds it impossible to obtain the desired standard of lighting. The results of this study will, however, indicate to him the allowance which should be made for such deficiencies in illumination.

The investigation is part of the research programme of the Building Research Board of the Department of Scientific and Industrial Research, and this note is published by permission of the Director of Building Research. The authors would like to acknowledge the help of their colleagues who assisted in the experimental work.

THE FORMATION OF THE INTRA-OCULAR FLUIDS. STUDIES OF THE UREA COMPONENT OF THE AQUEOUS HUMOUR

BY

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It has long been established that the concentration of urea in the aqueous humour is less than that in the blood plasma. After making allowance for the 7 per cent. difference in protein content between aqueous humour and plasma, the ratio of the urea concentrations of these two fluids has been determined by various workers using different chemical methods as follows:—

* R. S. Burnap and E. C. Jackson (1928). *Trans. I.E.S.* (U.S.A.), 23, 1153.

Species	Method	Mean ratio	
7 oxen	Urease-hypobromite	0.89	
7 dogs		0.82	
2 horses		0 87	
Horse (pooled aqueous and "typical" plasma)	Urease	0 94	E
14 cats	Urease-gasometric	0.75	Ad
10 dogs, 3 rabbits	Aeration-titration	0 70	Walker (1933)
1, dog, 2 cats 4 rabbits	Conductimetric	0.90	Benham (1937)
21 cats	Aeration Nesslerisation	0.73	Moore, Scheie and Adler (1942)
3 cats	Urease-Nesslerisation	0 77	Scheie, Moore and Adler (1943)
4 rabbits	Aeration-titration	0.66	Kinsey and Grant (1942)
14 rabbits... ...	Urease-diffusion	0.68	Kinsey and Robison (1946)

If the blood-aqueous barrier were a simple semi-permeable membrane and the aqueous humour a dialysate or ultrafiltrate of the blood plasma, non-electrolytes such as urea would be equally partitioned per unit volume of water between the plasma and the aqueous humour. The existence of a urea deficit in the intra-ocular fluids indicates that either the nature of the blood-aqueous barrier or conditions within the eye are such as to modify this equilibrium, by :—

(*a*) selective secretion of urea across the barrier out of the eye (Adler, 1933).

(*b*) utilisation of urea within the eye, or by

(*c*) the existence of a continuous bulk outflow of aqueous humour from the eye so that the rate of drainage of urea from the eye exceeds the rate of entry of this substance into the eye (Kinsey and Grant, 1942.)

In the present paper a kinetic study of the permeability of the blood-aqueous and blood-vitreous barriers to urea has been undertaken, the aqueous/plasma concentration ratio has been re-determined, the mechanism of entry of urea into the eye studied and evidence of utilisation of this substance investigated. Its

orde-
code of exit from the eye will be considered in a subsequent paper.

Part I—Kinetic Studies

The permeability to urea of the blood-aqueous barrier

Experimental

In order to demonstrate that the blood-aqueous barrier is permeable to urea a kinetic study of the transport of this substance from the plasma to the intraocular fluids was undertaken.

The principle underlying this type of experiment was to maintain a constant high blood-urea by continuous intravenous injection of an isotonic solution into an animal under pentabarbitone (Nembutal) anaesthesia. The renal vessels were tied to prevent rapid excretion of the substance during the injection. One eye was enucleated immediately before the initial injection to give a value for the initial urea concentration within the eye: a sample of blood was simultaneously taken from the femoral artery. An initial injection of 20 mls. of 6 per cent. urea was then made within one minute to raise the blood urea rapidly to a figure of between 100 and 200 mg./100 ml. H_2O, and further injections were made at intervals to maintain this high blood level since experience had shown that a stable level could be maintained by suitable boosts of urea solution. Samples of blood were removed at 10 minute intervals to check the constancy of this blood level. After a suitable interval (30 or 60 mins.) the other eye was enucleated and the final blood sample taken.

Fluids were removed from the eye as follows: aqueous was withdrawn from the anterior chamber, immediately after enucleation, by means of a clean, dry syringe; the vitreous body was obtained by freezing the enucleated eye in solid CO_2, cutting the frozen eye round the equator, removing the frozen vitreous with forceps, thawing it and forcing it through a glass wool filter to break up its gel structure.

Urea in this and all subsequent experiments was determined by the urease-micro-diffusion method of Conway (1946). This method was found to give consistent and accurate results with fluids of low and of high protein content, full recovery of added urea within 1 per cent. being obtained with plasma, aqueous and vitreous. The correction for plasma proteins was taken as 7 per cent. and all results are calculated as mg. per 100 mls. of water. In all experiments it is assumed that the urea content of the aqueous of a pair of normal eyes is identical; determinations of the urea contents of the aqueous of the two eyes of a pair show that this assumpion is justified within 1 per cent.

Results

Detailed results are presented in Table I. These results have been calculated in terms of the permeability constants for aqueous humour (K_A) and for the vitreous body (K_V) as defined by Davson and Quilliam (1940), where $K = 100 \cdot \log \dfrac{(S - A_1)}{(S - A_2)} \cdot \dfrac{1}{(t_2 - t_1)}$ (S = mean plasma urea concentration; A_1 = initial aqueous urea concentration at time t_1; A_2 = final aqueous urea concentration at time t_2. Time is expressed in hours.)

The results show that the rate of penetration of urea into the aqueous is consistently higher than that into the vitreous: mean $K_A = 11{\cdot}9$, mean $K_V = 5{\cdot}4$.

TABLE I

KINETIC STUDIES—RATE OF PENETRATION OF UREA INTO THE EYE (CAT)

(*a*) *Penetration into the aqueous humour.*

The permeability constant $K_A = 100 \log \frac{(S - A_1)}{(S - A_2)} \cdot \frac{1}{(t_2 - t_1)}$

(Concentration of urea expressed as mg/100 g H_2O)

Expt.	Blood 1	Blood 2	Aqueous 1	Aqueous 2	Time (mins.)	K_A
10	72.0	124.3	52.0	63.1	33	13.2
12	58.0	94.2	45.6	50.8	32	9.4
13	21.1	68.2	15.8	23.2	30	13.2
15	70.1	169.8	57.0	67.8	30	8.7
16	53.2	154.7	35.0	45.8	30	8.2
17	48.3	85.9	54.2	61.0	30	20.8
21	81.6	149.5	68.9	81.4	30	14.6
23	45.6	114.0	35.1	67.5	122	13.2
27	59.9	214.5	36.3	92.7	123	8.1
28	55.6	131.7	43.5	55.4	33	11.2
29	58.6	171.6	46.3	98.3	123	11.3
30	88.3	180.7	90.4	127.1	120	11 3
31	75.0	135.4	64.7	95.5	122	12.2
					Mean	11.9 ±1.5

(*b*) *Penetration into the vitreous body.*

Permeability constant $K_V = 100 \log \frac{(S - V_1)}{(S - V_2)} \cdot \frac{1}{(t_2 - t_1)}$

(Concentration of urea expressed as mg/100 g H_2O)

Expt.	Blood 1	Blood 2	Vitreous 1	Vitreous 2	$t_2 - t_1$ mins.	K_V
23	91.2	225.6	69.5	113.0	122	7.0
27	59 9	214.5	39.3	83.6	123	3.6
28	55.6	131.7	24.9	29.3	33	3.5
29	58.6	171.6	48.0	73.4	123	4.9
30	88.3	180.7	69.5	94 6	120	5.5
31	75.0	135.4	62.6	85.9	122	8 2
					Mean	5.4±0.6

Part II—Static Studies

(*a*) THE AQUEOUS/PLASMA RATIO

Experimental

Fluids were removed simultaneously from animals under pentabarbitone anaesthesia by the methods already described.

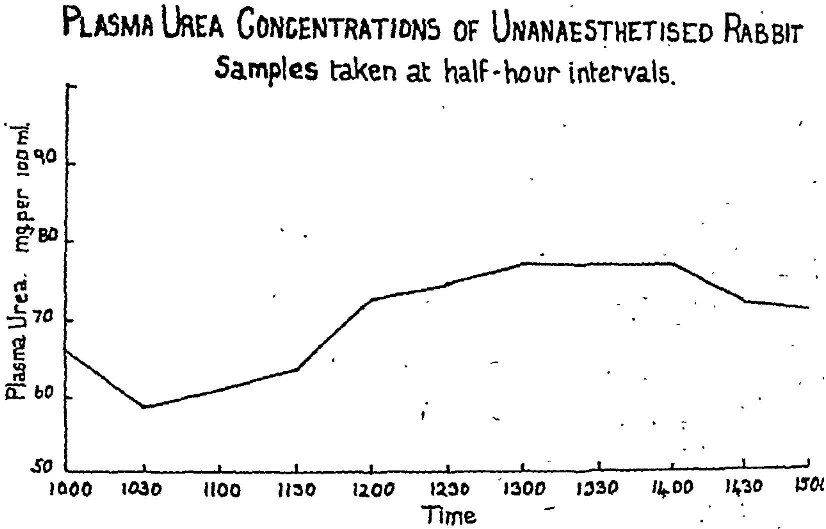

FIG. 1.

A study was also made of the fluctuations of the blood urea level in th unanaesthetised animal by taking blood samples at half-hourly intervals. Th results, which are plotted in Fig. 1, show that in the course of 3 hours the ure concentration varied between 59 and 78 mg. per cent., a difference of 24 per cent which will account for the wide scatter of the experimental ratios since change of urea concentration in the aqueous will lag behind the changes in the blood

TABLE II

THE DISTRIBUTION OF UREA BETWEEN BLOOD PLASMA, AQUEOUS HUMOUR AND VITREOUS BODY OF CATS

(Concentration of urea expressed as mg/100 g H_2O)

Expt.	Plasma	Aqueous	Vitreous	Aqueous/Plasma	Vitreous/Plasma
9	57.7	45.7	51.4	0.80	0.89
10	72.0	52 0	44.1	0.72	0.61
12	58.0	45.6	44.9	0.78	0.77
13	21.1	15.8	—	0.75	—
15	70.1	57 0	—	0.81	—
16	53 2	35.0	—	0.66	—
18	32.6	22.6	—	0 69	—
20	30.2	25.4	—	0.84	—
21	81 6	68.9	—	0.84	—
23	45.6	35.1	34 7	0.77	0.76
25	47.1	35.0	34.2	0 76	0.73
27	59.9	36.3	—	0.61	—
28	55.6	43.5	—	0.78	—
29	58.6	46.3	48.0	0.79	0.82
31	75.0	64.7	62.6	0.86	0.83
			Means	0.76±0.013	0.77±0.012

THE DISTRIBUTION OF UREA BETWEEN THE BLOOD PLASMA AND AQUEOUS HUMOUR OF RABBITS

Expt.	Plasma	Aqueous	Aqueous/Plasma
45	40.4	31.0	0.76
47	74 8	59.9	0.80
48	48.7	32.8	0.68
50	54.0	40.5	0.74
51	65.8	52.2	0.79
53	31.0	25.4	0.79
54	48.5	34.0	0.70
55	52.0	37.4	0 72
57	71.9	50 3	0.74
58	66.5	52.5	0.79
		Mean	0.75±0.02

Results

The distribution of urea between aqueous humour, vitreous body and plasma is shown in Table II. The existence of a deficit of urea in the intra-ocular fluids compared with the plasma water is confirmed. The mean aqueous/plasma ratio of 15 cats was found to be 0·76, that of 10 rabbits 0·75; the mean vitreous/plasma ratio of 7 cats was 0·77. Infinity values obtained by maintaining the blood concentration at a high level for many hours showed *that apparent equilibrium between the two fluids had been re-*established at the end of 3½ hours: this infinity ratio had a mean value of 0·73.

(*b*) THE UTILISATION OF UREA WITHIN THE EYE

Urea is regarded as the end-product of nitrogen catabolism in the mammal, and no evidence has so far been adduced that this substance plays any part in the synthetic processes of the body. The possibility that the difference in the urea concentration of blood and intra-ocular fluids may be due to utilisation within the eye by the metabolic activities of the lens, ciliary body or retina was nevertheless explored by both *in vitro* and *in vivo* experiments.

IN VITRO EXPERIMENTS

Study of the exchange between the lens and its environment was made with lenses excised from the enucleated eyes of rabbits and cats.

Assuming (1) that urea enters the eye by a process of diffusion, secretion, or filtration, not yet fully elucidated, and is removed by drainage, (2) that the urea concentration of the fluid crossing the blood-aqueous barrier is identical with that of plasma, (3) that the drainage rate from the anterior chamber is 4 c.mm. per min. (Kinsey and Grant, 1942; preliminary results of studies in this laboratory indicate that the rate is much higher in the cat), and (4) that the blood urea concentration is 40 mg. per cent., that the aqueous/plasma ratio is 0·75, and (5) that the volume of aqueous humour in the cat is 1·0 ml., then the quantity of urea entering the eye per hour is

$$\left(\frac{40}{100} \times \frac{4}{1{,}000} \times 60 \right) \text{mg.}$$

and the quantity leaving the eye per hour is

$$\left(\frac{30}{100} \times \frac{4}{1{,}000} \times 60 \right) \text{mg.}$$

It follows that the quantity of urea removed per hour from the aqueous humour between its entrance to, and its exit from, the eye will be

$$\frac{(10 \times 4 \times 60)}{10^5} \text{ mg.} = 0{\cdot}024 \text{ mg. per hour.}$$

If the metabolic activity of the lens is the factor responsible for the removal of urea from the aqueous so as to account for an aqueous/plasma ratio of 0·75, then the surviving lens immersed in a physiological medium containing urea should remove urea from this medium at a constant rate of 0·024 mg. per hour.

Experimental

The lens was removed from the excised eye, dried on filter paper and weighed, the whole procedure occupying less than 10 minutes. It was then transferred to a specimen tube containing fresh ox aqueous from eyes obtained from a slaughter-house and kept on ice until used; to this medium at pH 7·4 urea was added to give the required concentration. In the first set of experiments the lenses were incubated for 24 hours at 0°C., in subsequent experiments the incubation time was 2 hours at 37°C.; there is no obvious criterion of viability of a lens, and it was considered probable that the survival time of an isolated lens even in a physiological medium is a matter of a few hours only.

The urea concentration of this ox aqueous medium was fortified by added urea so that samples containing approximately 20, 50 and 80 mg. per cent. were obtained: the 2 ml. quantities employed in each experiment would thus contain 0·4, 1·0 and 1·6 mg. of urea respectively. After incubation for the required time the urea concentration of the medium and of a blank control of the same solution was determined.

TABLE III

EXPERIMENTS ON SURVIVING CAT LENSES INCUBATED FOR A STATED TIME AT A STATED TEMPERATURE IN OX AQUEOUS CONTAINING VARYING UREA CONCENTRATIONS TO SHOW THE QUANTITY OF UREA EXTRACTED FROM OR ADDED TO THE MEDIUM BY THE LENS DURING INCUBATION

(Urea concentrations expressed as mg/100 g H_2O)

Urea conc. of aqueous of eye from which lens was excised	Urea conc. of medium before incubation	Urea conc. of medium after incubation
(i) Incubation for 24 hrs. at 0°C.		
57.0	49.7	44.9
57.0	49.7	51.1
50.3	50.5	53.3
50.3	49.7	52 5
(ii) Incubation for 2 hrs at 37°C.		
53.6	80 8	62.5
53.6	80.8	59.9
40.1	79.1	47.9
40.1	79.1	49.6
50.0	49.1	50.8
50.0	49.1	53.4
40.1	49.1	51.4
40.1	49.1	56.5
25.1	15.6	18 7
25.1	15.6	19.3
20.3	18.6	25.1
20.3	18 6	24,0

Results

Detailed results are presented in Table III. They show that such differences as exist in the urea concentration of the medium before and after immersion of the lens in it for two hours can be accounted for by diffusion of the substance from a medium with higher, to a medium with lower concentration of urea; thus urea is removed by the lens from the medium when this contains a high concentration of the substance, but is added to the medium when the urea concentration of the medium is below that of the aqueous with which the lens was previously in equilibrium.

IN VIVO EXPERIMENTS

(i) ON THE EXCISED EYE

Experimental

The question of the utilisation of urea by the structures within the eye was further investigated by removing both eyes from the animal (rabbit) within as short a space of time as possible, evacuating the aqueous from one of the pair

immediately and determining the urea concentration of this fluid. The fluid of the other eye was evacuated after it had been kept at 37°C. for two hours and its urea concentration determined. *Any difference in the urea concentration of* the aqueous in the two eyes would indicate utilisation of urea within the eye by such vital processes as continued to function.

TABLE IV

EXPERIMENTS ON THE EXCISED EYE SHOWING THE UREA CONCENTRATION OF THE AQUEOUS HUMOUR OF A PAIR OF EYES, ONE AT THE TIME OF EXCISION AND THE OTHER TWO HOURS AFTER EXCISION. (RABBITS).

(Urea concentration expressed as mg/100 g H_2O)

Urea conc. of aqueous in two eyes of a pair	
(i) at time of excision	(ii) 2 hrs. after excision
65.2	64.0
45.8	44.0
56.5	54.9
44.0	43.5
49.2	48.0

Results

Results are presented in Table IV: these show that the differences in concentration initially and at the end of the two hours are too small to account for a utilisation sufficient to lower the aqueous urea concentration to 25 per cent. below that of blood. The volume of a rabbit's aqueous is about 0·25 ml. so that a difference of 1·2 mg. per cent. represents a loss of only 0·0015 mg. per hour: the theoretical rate to achieve the 25 per cent. deficit is 0·006 mg. per hour.

(ii) EXPERIMENTS ON THE APHAKIC ANIMAL

Experimental

If the lens is the factor responsible for removing urea from the intra-ocular fluids, the aphakic eye will show an aqueous/plasma ratio which approaches unity.

The lens of one eye was removed in a series of five rabbits by the standard surgical procedure for extra-capsular extraction. After an interval of six weeks to allow for complete healing, fluids were withdrawn from both eyes simultaneously and a blood sample obtained from the aural vein. Utilisation of urea by the lens would result in a lower concentration of urea in the unoperated eye compared with the aphakic eye.

Results

Results presented in Table V show that the unoperated eye consistently contained a slightly lower urea concentration than did the aphakic eye. The mean aqueous/plasma ratio of the

TABLE V

EXPERIMENTS ON THE APHAKIC EYE. UREA CONCENTRATION OF AQUEOUS HUMOUR IN THE NORMAL AND THE APHAKIC EYE OF A PAIR. (RABBITS).

(Concentration of urea expressed as mg/100 g H_2O)

Plasma	Normal eye	Aqueous/Plasma	Aphakic eye	Aqueous/Plasma
33.3	25 4	0.76	27.7	0.83
71.2	55.3	0.77	57.1	0.80
46 3	36 6	0.79	37.9	0.82
89.8	68 9	0.76	71 2	0.80
61.0	44.5	0.73	47.5	0.78

normal eye is 0·76, that of the aphakic eye is 0·81; although the aqueous/plasma ratio is raised in the aphakic eye it has not become sufficiently close to unity for utilisation of urea by the lens to be the explanation of the urea deficit within the eye.

Part III—The rôle of ultrafiltration in the formation of the intra-ocular fluids

(In collaboration with E. Bárány*)

Kinsey and Grant (1942) conclude from their study of aqueous humour dynamics that electrolytes are secreted across the blood-aqueous barrier but that water and non-electrolytes enter the eye by ultra-filtration. For ultra-filtration to separate a fluid from the blood against the colloid osmotic pressure of the blood (about 25 mm. Hg) and against the intra-ocular pressure (25-30 mm. Hg) a capillary pressure greater than 50-55 mm. Hg would be required: the greater the capillary pressure above this level the greater will be the rate of ultra-filtration. In the absence of any compensatory mechanism stabilising capillary pressure (and observations by Bárány of the capillaries of a rabbit's ear have revealed no such mechanism) any alteration of arterial pressure will materially affect the driving force across the membrane and, therefore, the rate of ultra-filtration. A measure of the part played by ultra-filtration can thus be obtained experimentally by variation of this pressure factor.

Reduction of the local capillary pressure and of the intra-ocular pressure can be produced by carotid ligation. As previously shown by Bárány (1946, 1947*a*) ligation of one common carotid in rabbits causes a fall of blood pressure, as measured in the

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central artery of the ear, of the order of 30-40 per cent. and a fall of intra-ocular pressure of 15-20 per cent. on the affected side for a period of at least 24 hours. If ultra-filtration is a significant factor such a fall of blood pressure could be expected to cause a considerable reduction in the rate of aqueous flow and hence in the rate of entry of water into the eye, an effect which should result in a rise in the urea concentration of the aqueous. Unilateral carotid ligation was accordingly performed upon a series of 10 rabbits, and the urea concentrations of the aqueous of the normal and affected eye compared.

Experimental

The common carotid artery was tied on one side in rabbits under pentabarbitone anaesthesia, the van Leersum loop technique being employed. After 24 hours, when the animals had completely recovered, they were killed by decapitation and the aqueous removed from both eyes as quickly as possible. Arterial blood was collected from the neck.

TABLE VI

THE EFFECT OF REDUCING THE ARTERIAL PRESSURE BY CAROTID OCCLUSION UPON THE UREA CONCENTRATION OF THE AQUEOUS HUMOUR OF RABBITS.

(Concentration of urea expressed as mg/100 g H_2O).

Expt	Side tied	Plasma	Aqueous on untied side	Aqueous on tied side	Difference Tied — Untied	Duplicates agreed within	Ratio $\frac{\text{Aqueous}}{\text{Plasma}}$
45	L	80 9	62 1	69.3	+ 7 mg %	2 %	0.76
47	L	74.8	59.9	66.6	+ 7 mg %	2 %	0.80
48	L	48.7	32.8	37.8	+ 5 mg %	3 %	0.68
50	L	54.0	40.5	39.5	— 1 mg %	1 %	0.74
51	L	65.8	52.2	48.0	— 4 mg %	2 %	0.79
53	R	31.9	25.4	26.6	+ 1 mg %	3 %	0.79
55	R	48.5	34.0	30.6	— 3 mg %	1 %	0.70
55	R	52.0	37.4	38.4	+ 1 mg %	2 %	0.72
57	R	71.9	50.3	53.6	+ 3 mg %	2 %	0.74
58	R	66.5	52.5	51.4	— 1 mg %	3 %	0.79
						Mean	0.75 ± 0.02

Results

Results are presented in Table VI. These show that lowering the systemic blood pressure by carotid ligation has no significant influence on the concentration of urea in the aqueous; the ratio of concentrations of aqueous (occluded) to aqueous (control) = 1·028 ± 0·025.

Discussion

The blood-aqueous barrier has been shown by kinetic studies to be permeable to urea although the rate of penetration of this substance into the eye is slower than that of water, of other non-electrolytes such as ethyl alcohol, glucose, or glycerol and corresponds with that of other nitrogenous substances such as creatinine, glycine or alanine. The permeability constants of these substances are compared in Table VII.

This relatively slow rate of penetration is surprising in view of the rapidity with which urea penetrates membranes in other parts of the body, *e.g.*, it penetrates the red cell envelope 35 times faster than does glycerol and yet its apparent rate of entry into the eye is only half that of glycerol. If entry into the eye occurred by

TABLE VII

COMPARISON OF PERMEABILITY CONSTANTS K_A AND K_V.

Substance	K_A	K_V	Species	Reference
Water ...	c. 300	—	Rabbit	Recalculated from Kinsey, Grant and Cogan (1942).
Ethyl alcohol	c. 90	—	Rabbit	Recalculated from Palm (1947).
Glucose ...	34	11	Cat	Davson and Duke-Elder (1948).
Glycerol ...	22	5	Cat	Davson, Duke-Elder, Maurice, Ross and Woodin (in press).
Creatinine ...	14	1.9	Cat	Ibid.
Glycine ...	13.5	1.0	Cat	Ibid.
Alanine ...	12.7	0 8	Cat	Ibid.
Urea	11 9	5.4	Cat	—

ultrafiltration across a semipermeable membrane through large water-filled pores, non-electrolytes should have a permeability constant which is proportional to the square root of their molecular weights (Davson and Danielli, 1943). Davson and Duke-Elder's (1948) studies of the permeability constants of carbohydrates suggest that these substances pass into the eye at rates inversely proportional to their molecular size. The urea molecule is only one-third as large as that of glucose and yet the glucose molecule enters the eye three times as fast as urea, a fact suggesting that in the case of urea some activity other than a process of ultrafiltration

is involved. Paracentesis of aqueous from the anterior chamber temporarily deranges this selective permeability of the barrier so that the urea concentration of the reformed "secondary" aqueous is at first equal to that of the plasma water, slowly falling to normal within the succeeding 24 hours.

The blood-vitreous barrier has been found to be even less permeable to urea than is the blood-aqueous barrier, the respective permeability constants being 5·4 and 11·9.

Re-determination of the aqueous/plasma and vitreous/plasma concentration ratios has confirmed previous observations that a deficit of the order of 20 per cent. exists between the intra-ocular fluids and the plasma water; an aqueous/plasma ratio of 0·76 was found in the cat and of 0·75 in the rabbit: the vitreous/plasma ratio was 0·77 in the cat.

The existence of this deficit in the intra-ocular fluids might indicate that urea was *entering the eye by ultrafiltration* and was being removed by entering into the metabolism of the lens or other structures within the eye. This possibility has been examined by a comparison of the aqueous/plasma ratios of the normal and the aphakic eye in rabbits, by *in vitro* studies of the lens and also of the excised eye, but *no evidence for any utilisation* of urea has been found.

The respective contributions of ultrafiltration and secretion to the formation of the aqueous have been studied by a method due to Bárány (1947*b*). If ultrafiltration were an important mechanism in aqueous formation then, following Kinsey and Grant's (1942) hypothesis, reduction in systemic blood pressure by unilateral carotid occlusion would cause a reduction in the rate of ultrafiltration which would show up as a rise in the urea concentration on the affected side. Such a rise cannot be demonstrated experimentally, from which it has been inferred that ultrafiltration plays little part in the formation of the aqueous humour.

These results are in agreement with the findings of Bárány (1947*b*) who found that reduction of blood pressure had no effect upon the rate of entry on Na^{24} into the aqueous. Bárány (1947*c*) later found that lowering the blood pressure likewise had no effect on the osmotic pressure of the aqueous such as would be expected to occur if ultrafiltration were playing a dominant part in aqueous formation.

These results suggest that some mechanism is present at the barrier to regulate the entry of fluid into the eye so as to maintain the aqueous flow constant irrespective of the systemic blood pressure.

The data presented in this paper thus show that the blood-aqueous barrier offers considerable resistance to the entry of urea

into the eye and that its rate of penetration is independent of the systemic blood pressure; the evidence obtained suggests that urea enters the eye by some process other than simple ultra-filtration.

Summary

(1) The urea concentration in the aqueous humour and the vitreous body has been found to be respectively 76 per cent. and 77 per cent. of that of the plasma water.

(2) The rate of penetration of urea into the aqueous and vitreous has been measured and the corresponding permeability constants calculated. These show that penetration into the aqueous is twice as rapid as into the vitreous and indicate that the blood-aqueous and blood-vitreous barriers offer considerable resistance to the passage of urea from the blood to the intra-ocular fluids.

(3) The urea deficit within the eye is not due to utilisation by structures within the eye.

(4) The rate of penetration into the aqueous has been shown to be independent of the systemic blood pressure and the evidence presented suggests that the substance is transferred across the blood-aqueous barrier by a process other than simple ultra-filtration.

I am indebted to Sir Stewart Duke-Elder and Dr. Hugh Davson for their interest and advice.

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OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

THE Annual Congress of the Society, which was held from March 31 to April 2 at the Royal Society of Medicine, was attended by 204 members and 91 visitors. Mr. Frank A. Juler presided over this happy gathering, whose success augurs well for the International Congress to be held in London next year. Many distinguished foreign visitors attended, some of them old friends of the Society. From Utrecht came Professor H. J. M. Weve. The Swiss visitors were Professor Marc Amsler, Professor A. Franceschetti, Dr. B. Semadini and Dr. N. Chomé. Dr. E. Hartmann, although paying his first visit to the Congress, was particularly welcome not only by reason of his official position, but also for his own charm. He has succeeded Dr. P. Mérigot de Treigny as Secretary-General of the Société française d'Ophtalmologie. Other welcome visitors from France were Professor G. P. Sourdille of Nantes, Dr. L. Paufique of Lyon and Dr. S. Vallon of Paris. We were also delighted to see Dr. Professor V. Rossi of Pisa, Professor G. B. Bietti of Pavia, Dr. R. Castroviejo of New York, Dr. A. Fritz of Brussels, Dr. A. C. Copper of Leiden, Dr. J. I. Barraquer of Barcelona, Drs. G. Karpe and J. Ollers from Stockholm, Dr. E. Palm of Lund, Dr. A. Mohn of Oslo, Dr. S. J. Braathen of Stavanger, Dr. B. Nyquist of Bergen, and Dr. H. Skydsgaard of Copenhagen. One pleasant surprise was the arrival from Spain of Dr. Arruga junior, on his way to Leeds, where he will be working with Mr. John Foster. A last-moment illness unfortunately prevented Professor M. A. El Kattan Bey, Dean of the Faculty of Medicine at Cairo, from attending the Meetings.

At the opening session the President extended a cordial welcome to ophthalmologists from abroad, and announced that future Bowman lecturers will receive a medal. Although there was not to be a Bowman lecture this year, medals had already been cast for presentation to former recipients of this honour, and he was glad that three of them were able to receive their medals in person. Sir John Parsons, F.R.S., whose Bowman lecture on the Foundations of Vision was delivered in 1924, stepped forward to receive the token, and was followed by Professor H. J. M. Weve (1939) and Professor Marc Amsler (1948). The President then announced that medals would be despatched to the other living Bowman lecturers—namely, Sir Arthur Keith (1930), Professor van der Hoeve (1932) and Dr. Arnold Knapp (1946).

The subjects considered by Mr. Juler in his Presidential Address were Some Points in the Operation for Acute Glaucoma and some Reflections on Refraction. Corneal Grafting had been chosen as

the content of the main discussion, and the Honorary Secretaries succeeded in assembling a galaxy of world-famous keratoplasticians. Professor Franceschetti, who opened the discussion, was followed by Mr. Tudor Thomas. Professor Sourdille, Dr. Paufique, Dr. Castroviejo, Dr. Barraquer, Dr. Fritz and Professor Bietti all produced interesting observations, and the other openers among British ophthalmologists were Mr. B. W. Rycroft and Mr. D. P. Choyce. Several most illuminating films were shown, and admiration was expressed for Dr. Castroviejo's astonishingly clear colour-photographs. This year the Society was particularly fortunate in the contributions made by people outside its speciality, because Dr. S. P. Meadows and Dr. Macdonald Critchley both read fascinating papers on neuro-ophthalmology, and Mr. D. N. Matthews gave a masterly, richly illustrated survey on the Technique of Plastic Operations in the Neighbourhood of the Orbit.

Abstracts of the above-mentioned and of additional papers will be published in *Ophthalmic Literature*. No clinical meeting was held, because the numbers attending Ophthalmological Society of the United Kingdom Congresses are now too large to permit examination by more than a minority of the members. The substitute plan of arranging a series of illustrated case-descriptions was voted a great success. Dr. Spence Meighan occupied the chair for the President on this occasion.

Professor Franceschetti proposed the toast of the Society after the Annual Dinner held at Grosvenor House on March 31. He reminded us of the close ties of friendship which have linked and still link British with Swiss ophthalmology. In replying to this toast the President referred in terms of warm appreciation to the kindness shown by Professor Franceschetti and by other hosts in Switzerland, France and Holland towards the parties of British ophthalmologists visiting foreign clinics under the auspices of the Faculty of Ophthalmologists. The official guests at the Dinner included Lord Webb-Johnson (President of the Royal College of Surgeons), Sir Henry Dale, F.R.S. (President of the Royal Society of Medicine), Dr. C. Thackray Parsons (Deputy Master of the Society of Apothecaries), Sir Stewart Duke-Elder (President of the Faculty of Ophthalmologists), Mr. F. A. Williamson-Noble (Master of the Oxford Ophthalmological Congress), Mr. D. N. Matthews, Dr. Macdonald Critchley and some of the above-mentioned foreign guests accompanied by their wives. Lord Webb-Johnson and Dr. Macdonald Critchley replied to the toast of the Guests, which had been proposed by Mr. J. H. Doggart. The President's health was proposed in terms of affectionate respect by one of his former house-surgeons at St. Mary's—Miss Ida Mann.

On April 1, a number of the foreign ophthalmologists and their wives were entertained to dinner by the Council of the Faculty of

Ophthalmologists at Apothecaries Hall, where they were received by the President of the Faculty and Lady Duke-Elder. After dinner Sir Stewart Duke-Elder's words of welcome were followed by a short survey of old customs and institutions in the City of London, given by Mr, Frank Law, the Honorary Secretary of the Faculty.

It was felt on all sides that this 1949 Congress went well. Certainly the President communicated a spirit of quiet enjoyment and welcome, and the arrangements made by the Honorary Secretaries and by the Secretariat at 45, Lincoln's Inn Fields made for smooth working of the social occasions as well as the scientific programme. Sincere gratitude has also been expressed to Lord Webb-Johnson, whose invitation to distinguished ophthalmologists from abroad to lecture at the Royal College of Surgeons served two important purposes. We were thereby encouraged to prolong the delights of the Congress, and we were permitted to hear four stimulating talks by Professor Weve, Professor Franceschetti, Dr. Hartmann and Professor Bietti.

FACULTY OF OPHTHALMOLOGISTS

The following is the Honorary Secretary's summary of the business conducted at the last Council meeting on February 18:—

It was learnt that the proposed enquiry into the working of the Supplementary Ophthalmic Service had been postponed. It was reported that following a meeting of the Ophthalmic Negotiating Committee the Ministry had decided to reduce the fee from £1 11s. 6d. to £1 5s. as from April 1 next, and that the turnover should be in the neighbourhood of 5 patients in two hours. The Minister proposed to discuss further with the profession the question of an investigation into the average time taken, and an undertaking had been given that the reduced fee should be suitably adjusted if its reduction was found to be unjustified. The matter was discussed at length and it was decided that the Negotiating Committee should be urged to protest against the reduction, and that each individual member of the Faculty should receive a copy of the Minister's letter with a letter explaining the position.

Mr. Duthie and Mr. Greeves have been elected members of the Standing Ophthalmic Advisory Committee for the National Health Service.

It was decided to send a circular letter to the Senior Administrative Medical Officers of Regional Hospital Boards urging them to set up Ophthalmic Advisory Committees if they had not already

done so, and giving an outline of the constitution of such a Committee. It was further arranged that representatives of the Faculty should call upon the Senior Administrative Medical Officers of Regional Hospital Boards and explain any points which needed explanation.

There were many points in the memorandum from the Joint Emergency Committee (Optical Profession) on the Ministry of Health directive, HMC(48)63, BG(48)66, to which the Council took exception, notably those arising out of the assumption that the report of the joint Sub-Committee of the Faculty and the Joint Emergency Committee represented the views of the Faculty, when in point of fact the Council had repudiated the report. The Honorary Secretary was instructed to write to this effect to the Senior Administrative Medical Officers of the Regional Hospital Boards and to Mr. Giles, Secretary of the Joint Emergency Committee (Optical Profession), and to inform the Ministry that he had done so.

After discussion and some dissent the Council by a majority decision endorsed the suggestion which had been made by the Ministry that the advisability of registration of opticians need not be discussed seeing that the Ministry were prepared to alter the constitution of the Committee to discuss the remaining quesion, *viz.*, the conditions of registration.

Mr. Davenport reported that he had received a copy of the amended memorandum on the training and examination of future entrants to the optical profession, together with a letter from Mr. Giles asking if it would be possible for opticians to attend hospitals during the final year of their training. It was agreed that this latter question could not be discussed until the recommendations of the Joint Advisory Board concerning the training and examination of opticians had been agreed. This memorandum had not been submitted officially to the Faculty.

In reply to a letter the Council suggested that the initiation of the Final Service would best be accomplished in the early phases by consultation with the Senior Administrative Medical Officer and the Ophthalmic Advisory Committee of the area concerned.

A letter was received from the British Medical Association, pointing out that the term of office of the members of the Ophthalmic Services Committees expired on March 31 and suggesting that the present members should be re-appointed. This was agreed.

The Council felt that no action could be taken in the matter of priority prescriptions for glasses in view of the fact that the machines in the country were already working to capacity.

The report was received of the Committee which had sat to consider the question of the examination of cases of miners'

nystagmus and heat cataract under the Workmen's Compensation Act. Mr. Healy explained the report, which was approved and filed with the documents.

Mr. Law reported that the Ministry was interested in the question of corneal graft donors and would be glad to meet representative members to discuss the situation. The following were appointed: Mr. R. C. Davenport, Mr. J. H. Doggart and Mr. A. Lister.

Letters were received from three members regarding alteration of the areas of the regions represented on the Council. The Council agreed that the present regions were unsatisfactory, and it was decided to consider the matter in detail at the next meeting.

NOTES

Gold Medal for the Prevention of Blindness

NEW YORK, March 23:—The Leslie Dana Gold Medal for 1948, a National award given annually for outstanding achievement in the prevention of blindness and the conservation of vision, was presented on March 25, at a dinner in St. Louis to Dr. Lawrence T. Post, Professor of Clinical Ophthalmology and head of the Department of Ophthalmology at Washington University Medical School.

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University of Glasgow Department of Ophthalmology. Whitsun Term. 1949

DURING May a series of meetings will be held in the Department on Wednesdays at 8 p.m. The general arrangements will be similar to the series held last year. A discussion will follow the main paper.

May 4, Prof. W. J. B. Riddell—"European Vacation"; May 11, Dr. Fergus Campbell—"Pupillary Movements"; May 18, Dr. Antoinette Pirie—"The structure of the Vitreous Humour"; May 25, Dr. W. O. G. Taylor—"Bleeding and Clotting within the Eye."

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OPHTHALMOLOGY

JUNE, 1949

COMMUNICATIONS

STUDIES ON THE INTRA-OCULAR FLUIDS

2.—The Penetration of Certain Ions into the Aqueous Humour and Vitreous Body*

BY

SIR STEWART DUKE-ELDER, H. DAVSON *and* D. M. MAURICE

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IN the first of this series of papers (Duke-Elder and Davson, 1949) a detailed study was made of the entry of sugars into the various parts of the eye from the blood; the present paper is a continuation of the same study with regard to salts. Exchanges of water between the blood and intra-ocular fluids occur rapidly, so rapidly as to indicate that these exchanges take place over a wide area of contact between the two systems and are not confined to a limited region such as the ciliary body. The osmosis of water into, or out of, the eye must influence the intra-ocular pressure immediately and effectively; and, since it is the salt content of the two fluids that

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* Dedicated to Professor J. Meller. Received for publication, February 14, 1949.

largely determines their osmotic pressures, the conditions under which salts may penetrate from the blood into the intra-ocular fluids are of fundamental importance. It has been shown from this laboratory that the osmotic pressure of the aqueous humour is greater than that of plasma (Benham, Duke-Elder and Hodgson, 1937) and again that the difference in osmotic pressure is due, at least in part, to an excess of sodium and chloride ions in the aqueous humour over that demanded by the Donnan equilibrium (Davson, Duke-Elder and Maurice, 1948). On these grounds, therefore, we may expect that sodium and chloride will be secreted into the eye, but whether or not the only mode of entry of these and other ions is by a secretory process from the ciliary epithelium is a matter that has not yet been decided.

THEORETICAL

It is hoped that kinetic studies on the mode of penetration of certain ions will throw some light on the problem, although in view of the formal similarity of certain equations for diffusion to those for secretion, it seems unlikely that a mere mathematical analysis of the process of penetration of a given ion can decide whether it is entering by a simple process of diffusion or secretion, or by a combination of these. The development of the mathematical formulae required here has been taken up elsewhere (Davson, Duke-Elder, Maurice, Ross and Woodin, 1949); for our purpose we need only indicate that the rate of penetration of a substance into the aqueous humour may be presented in the form of a parameter, K'_A, calculated from the experimental material by substitution in the following formula:—

$$\frac{r}{t} \log \frac{rC_p - C_{Aq_0}}{rC_p - C_{Aq}} = K'$$

where t is the time of penetration in hours, C_p and C_{Aq} are the concentrations of the substance in plasma and aqueous humour at time t; C_{Aq_0} is the original concentration in the aqueous humour and r is the ratio $\frac{C_{Aq}}{C_p}$ at infinite time. A parameter, K'_V, for penetration into the vitreous body, is computed similarly from the appropriate concentrations in this fluid.

The principal assumption at the basis of the derivation of the formula is that the penetration occurs in accordance with Fick's Law, *i.e.*, that the rate of transfer across the blood-aqueous barrier is proportional to the concentration gradient across the barrier.

METHODS

General. The operative technique was similar in essentials to that described earlier (Duke-Elder and Davson, 1949); a high and relatively constant concentration of a given substance was maintained in the blood of a cat anaesthetised with nembutal. This was achieved, in general, by a single intravenous injection of an isotonic solution followed by repeated smaller injections in accordance with empirically determined schedules which varied with the substance considered. In the case of radio-active potassium (K^{42}), however, the rate of loss from the blood was so rapid that it was impracticable to maintain a constant high level; consequently the solution was injected by a drip-infusion technique. The concentration of K^{42} rose rapidly during the first few minutes, and then more slowly and approximately linearly during the rest of the experiment. K'_A and K'_V were calculated by graphical integration. The eyes and blood samples were removed at appropriate intervals and the aqueous humour, vitreous body and plasma submitted to analysis.

Chemical. Thiocyanate was determined by the colorimetric technique of Aldridge (1945) on trichloracetic acid filtrates.

Radio-active Tracers. With the exceptions described below, all the determinations of radio-active tracers were done with the pipette-type counter described earlier (Maurice, 1948) and figured and described in Fig. 1. It was supplied with its high tension from a Dynatron Type 200 power unit, the counts being recorded on a Type 200 scale-of-ten scaler preceded by a modified Neher-Pickering circuit. The counter was always washed and dried between samples except when there was a reasonable certainty that their difference in activity was small. Sufficient counts were made to give a standard deviation of between one and two per cent. in case of plasma and aqueous humour, and of five per cent. in case of the vitreous body.

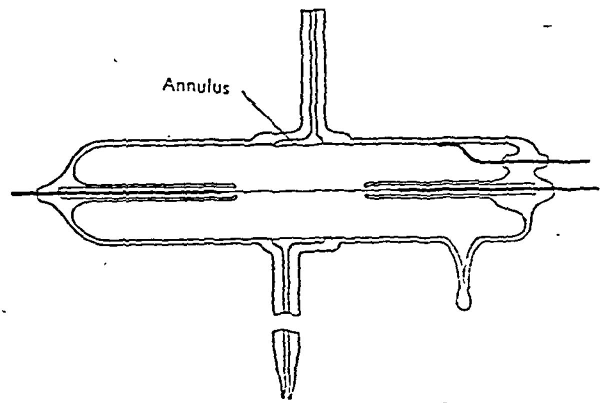

FIG. 1.

PIPETTE-TYPE GEIGER COUNTER FOR SMALL QUANTITIES OF BIOLOGICAL FLUIDS

The sample to be assayed (0·5 ml.) is sucked into the glass annulus which is formed round the cylindrical body of the counter itself and separated from it by a very thin glass wall. A high voltage is applied between the central wire and the wall of the counter, which is then sensitive to radio-active particles passing into it from the sample. These are individually registered on auxiliary apparatus. The number of particles counted in a given time is proportional to the concentration of the radio-active material in the sample.

Corrections were applied for the background count, the radio-active decay of the samples, and the resolution time of the counter. This last correction never rose above two or three per cent. The counter-voltage and the temperature were noted but they never varied sufficiently during an experiment to make a correction necessary.

In the case of the first five measurements of Na^{24} activity, the samples were measured into small glass dishes, which were stood on the window of a bell-type counter and located by means of a wax cast fixed by the edge of the window. Quadruplicate 0·2 ml. samples were used, the agreement being that expected from the number of counts taken.

For the first four phosphate determinations the sample, after removal of proteins if necessary, was treated with sufficient sodium phosphate solution to give about 1 mg. of precipitate, excess of magnesium and ammonium chlorides was added and the mixture made alkaline with ammonia. The precipitate of magnesium ammonium phosphate was collected by suction on a sintered glass filter, 4 mm. in diameter, sealed into the end of a glass tube. It was found necessary to repeat the precipitation on the first filtrate in order to complete the collection of the phosphate. The collected precipitate was dried and the "filter stick" was accurately positioned by a brass frame in proximity with the window of a bell-type counter.

Na^{24} was used in the form of sodium chloride with an activity of 1 mC per g.; K^{42} as potassium chloride of similar activity. P^{32} was received as a solution of phosphoric acid containing less than 10 mg. per ml. of total solids and with an activity greater than 0.3 mC per ml. and this was brought to pH 7·4 with NaOH.

TABLE I

THE RELATIVE RATES OF PENETRATION OF CERTAIN IONS INTO THE INTRA-OCULAR FLUIDS

Substance	No of Expts.	100 K'_A	100$'_V$	K'_A/K'_V
Thiocyanate	12	46·5 ± 2·3	18·3 ± 1	2·5
Sodium	15	37·6 ± 1·2	6·8 ± 0·3	5·5
Potassium	14	42 — 31	12 — 7·7	3·5 — 4
Phosphate	6	5·2 ± 0·9	0·33 ± 0·05	16

RESULTS

The *relative rates of penetration* of thiocyanate, sodium, potassium and phosphate into the intra-ocular fluids are shown in Table I. The differences in the rates of penetration are of considerable significance. In the first place the rate of penetration of thiocyanate is significantly greater than that of either sodium or potassium; and all three of these ions penetrate very much more rapidly than phosphate. The slow rate of penetration of the latter substance agrees with the results of a more exhaustive study by Palm (1948) on the rabbit. That thiocyanate enters more rapidly than sodium was confirmed by injecting both radio-active sodium and thiocyanate into the same animal, and measuring the rates of penetration of both. The mean of two experiments gave the following :—

	K'_A	K'_V
Sodium	34.4	6.8
Thiocyanate	43.7	20.7

A comparison of the rate of entry of thiocyanate and the sugars is also of interest. In the earlier paper of this series it was shown that the value of K'_A for the monosaccharides is, on the average, 32·5 and that for K'_V 11·2; it appears, therefore, that thiocyanate penetrates rather more rapidly than the monosaccharides into the aqueous humour and nearly twice as rapidly into the vitreous body. This is confirmed by simultaneous measurements on the same animal as is seen in Table II.

TABLE II

THE SIMULTANEOUS PENETRATION OF SUGAR AND THIOCYANATE INTO THE EYE OF THE CAT

Animal	Substance	100 K'_A	100 K'_V
No. 1	Thiocyanate	42·5	16·8
	Galactose	26·7	6·5
No. 2	Thiocyanate	40	20
	Glucose	27·1	7·8
No. 3	Thiocyanate	27·5	16
	Galactose	21·2	4·6

The variability of the rate of entry of potassium is noteworthy. In Table I the values of K′ for potassium have been indicated as a range varying between 42 and 31 for the aqueous humour and 12 and 7·7 for the vitreous body. This variability was due, in general, to the fact that the value of K′ determined from the first half-hour of penetration, was consistently greater than that obtained from the second half-hour. There is thus an unmistakable tendency for the rate of penetration of potassium to slow down during the course of the experiment under the conditions employed in this work. This matter is under investigation and will not be discussed further at present: the difference between the constants derived from the first and second half-hours of penetration is brought out by the following:—

K'_{A_1}	K'_{A_2}	K'_{V_1}	K'_{V_2}
40.5	30.3	11.8	7.4

which may be contrasted with the following figures for sodium:—

K'_{A_1}	K'_{A_2}	K'_{V_1}	K'_{V_2}
38.7	37.3	6.8	6.6

The site of penetration. In earlier experiments on the penetration of sugars (Duke-Elder and Davson, 1949) it was concluded that these substances entered the cavity of the eye from all the surrounding vascularized tissues. It will be remembered that this conclusion was based on the separate analysis of different sections of the frozen vitreous body. A similar technique was followed here, the frozen vitreous body being separated into three parts by sections at right angles to the antero-posterior axis, the anterior portion closest to

the ciliary body, the posterior part farthest away. If diffusion from the blood into the vitreous body occurred not only from the ciliary body but also from the whole of the posterior segment of the globe, the middle section would have the lowest concentration of the penetrating substance owing to the unfavourable area-volume relationship pertaining in this region. If, on the other hand, diffusion occurred exclusively from the ciliary body, the posterior portion would have the lowest concentration. As with the sugars

TABLE III

RELATIVE CONCENTRATIONS OF THIOCYANATE IN THE THREE SECTIONS OF THE VITREOUS BODY AFTER THE CONCENTRATION IN THE BLOOD HAD BEEN MAINTAINED AT A HIGH VALUE FOR VARIOUS TIMES

Time (min.)	Aqueous Humour	Concentration		Posterior
		Anterior	Middle	
30	100	46	49	46
30	100	55	64	82.5
31	100	47	34	55
34	100	39	28	33
38	100	53	37	64
60	100	58	42	44
60	100	55	37	57
60	100	56	52	80
60	100	68	68	80

TABLE IV

RELATIVE CONCENTRATIONS OF Na^{24} IN THE THREE SECTIONS OF THE VITREOUS BODY AFTER THE CONCENTRATION IN THE BLOOD HAD BEEN MAINTAINED AT A HIGH VALUE FOR VARIOUS TIMES

Time (min.)	Aqueous Humour	Relative Concentrations		Posterior
		Anterior	Middle	
28	100	44	12	18
60	100	38	29	25
7	100	27	12	6
8	100	24	11	10

it was found that with thiocyanate the middle sections, on the average, had the lowest concentration at the end of a given period of diffusion: the concentrations in the aqueous humour and the different parts of the vitreous body are as shown in Table III. One may tentatively conclude from these results, that thiocyanate diffuses into the vitreous body from all the vascularized tissue surrounding it. With radio-active sodium and potassium, on the other hand, a significantly different picture of distribution in the frozen vitreous body was obtained as is shown in Tables IV and V.

TABLE V

RELATIVE CONCENTRATIONS OF K^{+} IN THE THREE SECTIONS OF THE VITREOUS BODY AFTER THE CONCENTRATION IN THE BLOOD HAD BEEN MAINTAINED AT A HIGH VALUE FOR VARIOUS TIMES

Time (min.)	Aqueous Humour	Relative Concentrations		
		Anterior	Middle	Posterior
30·5	100	43	20	14
31	100	54	20	13
31	100	92	41	16
31	100	49	39	18
38	100	53	23	20
59	100	64	44	23
58	100	71	31	13

From these tables it will be seen that, with both sodium and potassium, by far the highest concentration is that found in the most anterior segment of the vitreous body which is in closest proximity to the ciliary body. The region having the smallest concentration is the most posterior segment which is farthest away from the ciliary body. From these findings it is difficult to escape the conclusion that penetration of sodium and potassium into the posterior segment of the eye is predominantly from the ciliary region.

DISCUSSION

We wish to discuss at present three points relating to the facts described in this paper. First, we have the observation that thiocyanate penetrates from the blood into the aqueous humour and vitreous body more rapidly than either sodium or potassium;

the difference in rate is particularly evident in respect to penetration into the vitreous body. This difference seems to rule out the possibility that the main route of penetration of salts is by water-filled pores as it is throughout the body generally, that is, by way of the inter-cellular spaces of the capillaries and the lining membranes of the eye. If this simple mechanism were responsible, the relative rates of penetration of the different ions would correspond with their ionic mobilities, *i.e.*, the values for sodium, potassium, and thiocyanate should be as 44 is to 65 is to 56. We may therefore conclude, on this count, that the factors of cell membrane permeability (lipoid solubility, adsorbability, etc.) play an important part in determining penetration into the intra-ocular fluids from the blood. It follows that, so far as these substances are concerned, *transference from the blood into the chambers of the eye takes place through cell bodies and not inter-cellular spaces,* a conclusion which is in conformity with the fact that the salt content of the aqueous humour is greater than can be accounted for by a simple process of ultra-filtration.

Secondly we may note that the relative rates of penetration into the aqueous and vitreous differ very considerably between the various substances studied. All the salts studied enter the vitreous more slowly than the aqueous, but while thiocyanate enters the former most easily, phosphates do so only in very small quantities. Thus the ratio K_A/K_V for the thiocyanate ion is 2·5 whilst for sodium and potassium it is in the region of 5 and for phosphate it is 16. It seems probable that these differences depend on the differing sites of penetration of the respective ions. The evidence presented here indicates that thiocyanate penetrates throughout all the vascularized parts of the eye, *i.e.*, from the entire uveal, and presumably the retinal, circulations while sodium and potassium penetrate into the posterior segment of the eye through a restricted area only—the ciliary region. If this is the case it is obvious that the rate of accumulation of the first substance in the vitreous body should be greater, other things being equal, than that of the latter two. It may be recalled here that the monosaccharides, which also appear to penetrate into the vitreous body from all parts of the barrier, gave a ratio of K_A/K_V of 2·9 which is comparable with that for thiocyanate. In discussing this point earlier (Davson and Duke-Elder, 1948), it was pointed out that, if the barrier between blood and vitreous body were more selective than that between blood and aqueous humour, we should expect the ratio of K_A/K_V to become greater, the slower the rate of penetration of a substance; thus with the sugars the ratio was 2·2 for a pentose; 3·3 for hexoses, and 17 for sucrose. The high ratio reported here for phosphate, namely 16, is probably due chiefly to this factor; the amounts

penetrating the vitreous body were so small that it was not feasible to estimate the separate amounts in different parts of the vitreous body and so to find out whether penetration was confined to the ciliary region or not.

A final word will not be out of place on the bearing of these results on the problem of the formation of the intra-ocular fluid. Such mathematical treatment as the results have been given has been on the basis of the assumption that the amount of substance entering the fluid in unit time is proportional to the concentration gradient at that moment; in other words it has been assumed that the penetration is determined by the simple physico-chemical laws of diffusion. With the possible exception of potassium, the experimental results conformed with the equations in the sense that the parameter K′ appeared to be independent of the concentration gradient and the time of penetration. One might be inclined, on the basis of this finding, to suggest that penetration of the salts discussed is predominantly a matter of simple diffusion. Such a conclusion, however, would be unjustified; it is easy, as Kinsey and Grant (1942) have shown, to establish an equation on the basis of a supposed secretory mechanism, which has essentially the same form as the one employed here and derived without any assumptions of secretory activity. Kinsey and Grant concluded that salts entered the eye by a process of secretion largely as a result of this conformity of their results with their arbitrary secretion equation, but it is quite evident that in the present state of our knowledge an appeal to the results of mathematical analysis unsupported by other evidence is not yet warrantable, since the same equation may be derived on the basis of such entirely different postulates (Bárány and Davson, 1948). It would seem, however, that since the concentration of salts into the intra-ocular fluids is higher than can be accounted for by a process of simple ultra-filtration, some cellular activity (that is, a process of secretion) in their transference must be postulated.

SUMMARY

1. The salt content of the intra-ocular fluids is greater than can be accounted for by a process of simple ultra-filtration. Some cellular activity is therefore involved in the transference across the blood-aqueous barrier: a process of secretion must be postulated.

2. The various electrolytes tested (sodium, potassium, thiocyanate) penetrate across the blood-aqueous barrier at varying rates which cannot be accounted for by a simple diffusion through inter-cellular spaces, but only by penetration through cell bodies.

3. While some ions (thiocyanate) penetrate into the intra-ocular fluids throughout the whole of the blood-aqueous barrier, others

(sodium) enter the posterior segment of the cavity of the eye (in large measure, at any rate) by way of the ciliary body.

All the thiocyanate determinations described in this paper were carried out by Mr. A. M. Woodin.

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DISEASES OF THE EYE IN RELATION TO DENTAL SURGERY*

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THE current fashion of labelling diseases " allergic " has to some extent diverted attention from focal sepsis. Nevertheless that controversy is still alive, and it would be safe to predict widely varying estimates if any twelve ophthalmologists were invited to answer the question: " What percentage of the ocular disease in your practice is due to unhealthy teeth ? " There are, of course, many other organs and tissues on which attention has been riveted by people seeking to explain inflammatory lesions of the eye. The vermiform appendix, the colon, the prostate gland, the skin and the tonsils have all been singled out for blame, and that list might be greatly extended.

In all the mass of literature dealing with ocular disease of supposedly dental origin, one feature has escaped comment, so far as I have been able to ascertain. I refer to the curious assumption that infective traffic between the teeth and the eyes must be one-way. When will some champion take up the cudgels on behalf of these much-maligned gomphoses? Such a man might begin by

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proclaiming his disbelief in dental iridocyclitis, and then, carrying the war into the enemy's camp, he would doubtless marshall statistics whereby ocular lesions could be indicted as a source of parodontal disease. The main weakness of this doctrine would be that it could hardly be carried to its logical end, because total extraction is so infinitely more drastic a policy when dealing with eyes than with teeth. No such objection, however, would arise if the blame were put upon the ocular adnexa, which consist of the eyelids and lacrimal apparatus. When once an observer had convinced himself that among the convolutions of the Meibomian glands lurked organisms more dangerous than those harboured by any other focus, he would soon be assembling cases in which treatment applied to the eyelids had been followed by dramatic amelioration of the dental state. He might even persuade his patients that they should go to bed with teeth uncleaned rather than neglect their lid-massage.

It may be well, however, to postpone this question of focal sepsis until we have considered some of the instances in which teeth and eyes are fellow-victims of (1) abnormal development, (2) trauma, (3) diseases of other organs and tissues, and (4) toxic hazards.

A. ASSOCIATED OCULAR AND DENTAL LESIONS

1. *Developmental defects* of the eyes and teeth are inevitable whenever there is widespread malformation of the head and face, but fortunately most of the resulting monsters are stillborn. More important from the practical standpoint are cases in which infantile lamellar cataract is associated with hypoplasia of the teeth. Theoretically these allied signs might be attributable to some defect in the germ-plasm—that is to say, they might be hereditary in the strictest sense; but most people interpret them as the effect of unfavourable intra-uterine influences, such as toxins derived from micro-organisms, or poisonous substances in the mother's food. Maternal diet can be the vehicle of damage not only through its noxious contents, but also by reason of deficiency. There might, for instance, be a shortage of certain essential amino-acids, vitamins or metals. Adequate calcium content is one well-recognised need during pregnancy, and the relationship of that element with the parathyroids is bound up with the influence of the latter upon the skeletal system. Parathyroid defect is closely linked with tetany and rickets, and the dental changes chiefly implicate the first molars together with the central and lateral incisors.

2. *Trauma*. One of the greatest therapeutic triumphs of modern times is the treatment of severe facial injuries, especially those accompanied by fracture of the upper-jaw. During the recent war

I visited the maxillo-facial units at Hill End, Park Prewett and East Grinstead, and also had the opportunity to see their successful end-results coming back into active service. Many a man hurtled against a wall in motor-cycle crashes would have been condemned to frightful disfigurement and enduring diplopia, had it not been for the skill of dental and plastic surgeons promptly administered. The ingenious devices whereby traction was applied to reinforce the action of splints after early reduction of those impacted maxillary fractures moved me to admiration, and there must be many medical men whose respect for the dental profession was enhanced by war-time contacts.

In the early stages of severe facial injury ophthalmic examination is needed with a view to ascertaining whether any immediate eye treatment is necessary, but thorough inspection is often impossible until swelling of the eyelids has abated. Later on the patient may require orthoptic and operative treatment for double vision due to weakness of one or more of the extra-ocular muscles, but spontaneous recovery from diplopia often ensues within a few weeks, if early manipulation by a dental expert has succeeded in restoring the alignment of the inferior orbital margin.

One possible result of maxillary trauma is an extension of sepsis from the teeth to the eyes, but the routes whereby infective material may travel will be considered later. Another possibility to be borne in mind is that ocular damage may be occasioned by a violent dental extraction. In this connection the myopic retina is particularly vulnerable. When we consider that the jolt of a starting train has been known to provoke retinal detachment, and that large haemorrhages may become evident on the surface of the fundus immediately after a sneeze, it is not surprising that similar havoc may accrue when jaws are wrenched against the resistance of muscular spasm. This last-mentioned state of affairs is apt to arise when a strong man undergoes incomplete dosage with nitrous oxide.

Before we leave the subject of trauma, it may be interesting to recall that a few of the dental surgeons attached to maxillo-facial units in the recent world war became expert in the construction of artificial eyes. In one instance I can testify to such skill on the part of a Service dentist, to whom I referred a number of cases needing prostheses. So far I have failed to trace any evidence of reciprocal virtuosity on the part of an ophthalmologist, and I doubt whether many of you would be inclined to delegate the building of your patients' dentures to an eye doctor.

3. *Diseases of other organs and tissues.* (*a*) *Endocrine dyscrasia.* Reference has already been made to the close relationship of the *parathyroids* with calcium metabolism, and we know

that other members of the endocrine orchestra can exert a profound influence upon dental and ocular welfare before and after birth. Thus the skeletal changes associated with *dyspituitarism* can interfere with the alignment of teeth, and the victim may also exhibit defects of the fields of vision due to pressure of the gland upon the optic chiasma or adjacent portions of the visual pathway.

The eruption of teeth is delayed in cretins, and further impairment is entailed by pressure from the heavy, splayed-out tongue typical of this disease, which in its turn is caused by hypoplasia of the *thyroid* gland. Further evidence that secretion from this gland affects the dental state is provided by the administration of thyroxin to experimental animals. Eruption of the incisors is thereby accelerated.

One disease that has often been found in association with widespread endocrine disturbance is *keratoconjunctivitis sicca*, a condition arising in middle life, and predominantly affecting women. It is characterised by sensations of dryness and grittiness of the eyes. Examination usually reveals irregularity of the corneal epithelium, together with small whitish strands of irregularly proliferating cells attached to the surface of the cornea. Absence of or diminution in the tears must be held partly responsible for the symptoms, but deprivation of the mucus normally secreted by small glands in the conjunctiva probably counts more. From the dental surgeon's standpoint the main importance of *keratoconjunctivitis sicca* is that similar desiccation usually occurs in the victim's mouth. Therefore she may become incapable of tolerating her dentures for more than a few minutes at a time.

(*b*) *Bone disease.* A number of bone diseases possess joint interest for dental and ophthalmic surgeons. *Acute osteomyelitis of the upper jaw* is one example which may arise in early infancy. Most people are agreed that ethmoidal suppuration is the commonest cause of orbital cellulitis among infants, but maxillary osteomyelitis, with or without preceding trauma to the mouth, should always be borne in mind as a possibility. Some of the reported cases have been fatal, but successful results have recently been claimed for penicillin therapy. Swelling and induration of the cheek on the affected side is a conspicuous sign, the temperature is high, and the infant usually looks very ill. When an abscess forms, it may point along the gum-line, on the palate, in the nose, or through the lower eyelid. Proptosis and restriction of ocular movement on the affected side are prominent features until the pus is absorbed or evacuated.

In *osteogenesis imperfecta* we find blue sclerotics associated with abnormal fragility of the bones, so that fracture of the lower jaw may arise from a relatively slight blow. The upper and lower jaw

may both be implicated in *Schüller-Christian xanthomatosis*, a disease which may produce proptosis of the eyeballs in early childhood. Slight fever, secondary anaemia, and diabetes insipidus due to hypopituitarism are other items in the clinical picture, and the diagnosis is clinched by radiography of the skull, the flat bones displaying punched-out areas of rarefaction. *Albers-Schönberg's disease* tends to run in families, and consists of diffuse osteosclerosis. One of its characteristic results is bilateral optic atrophy due to encroachment of the new-formed bone upon the optic canal. Delayed dentition and early caries are also noted, and occasionally osteomyelitis of one or both jaws supervenes. In *oxycephaly* the small size of the maxilla may interfere with dental development by crowding the teeth together. Delayed dentition is also a feature of *hereditary cleido-cranial dysostosis*, a disease in which defective ossification of the skull-vault lends to depression of the orbital roofs, and that in its turn produces exophthalmia.

Two bone diseases of later onset are worthy of mention. *Leontiasis ossea* is particularly apt to induce hideous deformity, because the two sides of the face are seldom symmetrically involved. Lateral and forward displacement of one or both eyes may become evident, and vision may be curtailed by pressure upon the optic nerve in its bony canal. Similarly the teeth may sustain damage and displacement from irregular encroachment of bone in the upper and lower jaws. In advanced cases the dental state may be aggravated by hindrance to closure of the mouth. *Paget's disease* is a familial affection of later life, often associated with generalised arteriosclerosis. Immense thickening occurs in the long and flat bones, and X-ray photographs in an advanced case reveal characteristic areas of adjacent absorption and calcification. In some cases the onset is exceedingly slow, and indeed this disease may stay mainly confined to one bone for many months. Probably the tibia is the commonest single bone to display Paget's type of thickening, but cases have been described in which signs were first exhibited in the maxilla. Sooner or later the orbital walls begin to thicken, and deposition of bone in the optic canal leads to progressive optic atrophy.

Skeletal and endocrine diseases have been briefly reviewed, because they supply so many striking instances of associated dental and ocular disturbance. Other kinds of linkage might readily be assembled, but here it will suffice to stress the interdependence of organs and tissues throughout the body. Clearly the eyes and the teeth are likely to last longer in people blessed with a sound cardiovascular system, and yet the finest heart and blood-vessels in the world cannot keep these organs healthy unless their nervous connections are intact—because all nerves are in a real sense trophic.

Nor can the nervous and circulatory structures function well, unless every essential item of diet is supplied in appropriate quantity. Thus the problem of causation in an apparently simple lesion may be complex beyond the bounds of imagination. Whatever facts may be elicited by clinicians working in close co-operation with dietetic experts, pathologists, radiologists and other specially trained helpers, we cannot explain every aspect of disease, because the mode of response to identical noxious stimuli may be largely conditioned by genetical factors impossible of assessment.

4. *Toxic hazards.* A few examples will serve to show how the eyes and teeth share susceptibility to a number of poisons. *Lead* can play havoc with the optic nerve and the jaws, but improved plumbing together with preventive industrial measures have almost eliminated this former scourge. Necrosis of the orbit and jaws from *phosphorus* is also rare to-day. Indeed so much knowledge has accumulated concerning the injurious by-products of mines and factories, that important chemical lesions seldom arise unless workers are unintentionally exposed to some new organic compound, the pharmacological effect of which is not yet appreciated. Many volumes have been written upon the deleterious effects of *nicotine* upon the eyes and teeth, and we cannot expect to find unanimity of opinion upon this question for many a year to come. Few would deny that excessive smoking injures the buccal mucous membrane, and incidentally the teeth, but wide individual variations in tolerance make one man's moderation another man's excess. Tobacco amblyopia is a real threat to heavy smokers in later life, and necessitates complete abstinence from smoking, but other factors besides tobacco play a part in its development.

B. THE TEETH AS A SOURCE OF OCULAR INFECTION

It is abundantly clear that some disease-processes can spread from the teeth to the eyes, but wide disagreement exists concerning the proportion of dental infection compared with that from other sources. Theoretically dental disease could be communicated to the eye by direct extension through bone and other connective tissue, or along the ramifications of nerves, or *via* the veins and lymphatic vessels. Toxins might enter the blood-stream direct from diseased teeth and afterwards find their way into the ocular arteries; or the noxious material might travel indirectly, being absorbed into the blood-stream *via* the alimentary canal. Nor would it seem impossible for dental toxins to reach the inferior meatus of the nose, whence they can travel up the tear-passages into the conjunctival sac. Probably all or most of these pathways have been traversed by infective material, but dissemination by the blood-stream is

generally regarded as the most important, except in cases which plainly show direct spread.

Among the conditions which ophthalmologists have regarded as due to dental disease are orbital cellulitis, dacryocystitis, blepharitis and other inflammatory disorders of the eyelids, conjunctivitis, episcleritis, keratitis with or without ulceration, iridocyclitis, choroido-retinitis, venous thrombosis, cataract and lesions of the optic nerve. In this connection particular stress has been laid upon iridocyclitis, and the reasons are not far to seek. Cases of iridocyclitis exhibit astonishing variations in severity and duration, and incidentally, of course, in their apparent response to treatment. Some show slight initial changes, but keep on recurring until the eye is ruined. Others severely affected at the outset clear up rapidly, and then go on for years without further trouble. It follows therefore that *any* treatment will appear to produce miraculous results in a certain number of cases. Enthusiasts naturally resent being told that they have mistaken mere sequence for a cause-and-effect relationship, but such reminders are wholesome and necessary. In dealing with so variable a disease as iridocyclitis, we have to look askance at alleged therapeutic triumphs until the method in question has proved effective in a long series of carefully followed-up cases.

Now the theory of focal infection, so long as it is firmly upheld, can be advanced as a coherent explanation for nearly all kinds of endocular inflammation, and positively disproved in hardly any instance. Let us imagine a case of iridocyclitis being examined in consultation with a colleague firmly convinced that teeth are nothing but fountains of sepsis. No clinical evidence of dental disease can be found. Then he points out that a healthy-looking tooth may be likened to a whited sepulchre. X-ray photographs are now prepared, but fail to reveal any abnormality. Our friend now proceeds to quote authority for his belief that radiographically negative teeth are by no means incapable of spreading disease elsewhere in the body. Thus he persuades the patient to part with his teeth, and one of three things happens:

(*a*) The eye recovers. That clinches the argument.

(*b*) The eye gets worse, but that goes to prove how wise it was to insist upon extraction. Exacerbation analogous to a Herxheimer reaction is readily interpreted as the effect of an extra dose of toxin flung into the circulation while the teeth were being dislodged.

(*c*) No change is noted in the eye. Therefore the offending teeth must have set up a secondary focus of infection before the patient had finally decided to part with them. Probably the prostate is now to blame, though admittedly palpation reveals no abnormality of that organ. Yes, but chronic prostatitis may drag on for

years without producing any localising signs or symptoms. Prostatectomy is now performed. Still the iridocyclitis grumbles on, because [*sic*] the original focus has impaired the patient's power of resistance, and he is now susceptible to the action of lesser toxins, which he would have taken in his stride had his defences not been undermined by those teeth.

Let me repeat that such a zealot cannot be decisively confuted at any stage in his argument, and my reason for setting-out that grim sequence of events is that I have often heard people argue on those lines. With very little modification the same kind of reasoning can be adduced to prove that any particular disease is an outburst of allergy—whatever that may be.

It would appear, however, that the concept of dental infection as a paramount factor in the production of intra-ocular disease has lost ground. Several research workers have failed to repeat the earlier work on apical infection, and it has been suggested that oral contamination would explain many disquieting statistics about the prevalence of streptococci in the teeth. It has also been shown that radiolucent areas around dental roots are not necessarily a sign of disease, and more and more people have come to believe that teeth should be treated on their own merits—or demerits, as the case may be. Was it not Don Quixote who said: "A diamond is not as precious as a tooth." My own attitude towards the relation of dental with ocular disease can be summarised as follows :

(1) Harmful substances can certainly pass from the teeth to the eyes, and possibly in the reverse direction.

(2) I do not believe that the teeth are mainly to blame in more than a small minority of the cases of ocular disease.

(3) The causation of disease is infinitely more complex than most people realised three or four decades ago, when the doctrine of focal sepsis was approaching the peak of its popularity.

In fairness to the dental surgeon, it should be pointed out that the indiscriminate slaughter of teeth as a measure of desperation in cases not responding to other forms of treatment has nearly always been at the instigation of medical men. Consider rheumatoid arthritis and recurrent iridocyclitis, which have several important features in common. Both are productive of much pain and disability. In each of these diseases the cause is complex and imperfectly known, so that the stage is set for the enthusiast whose attention is disproportionately directed to one aspect of the problem. Some cases of iridocyclitis display features which an experienced clinician can recognise as pathognomonic or at least strongly suggestive of syphilis, gonorrhoea, tubercle and various other diseases. Corroboration is in many instances supplied by the

manifestations of a similar pathology elsewhere in the body. Nevertheless it remains true that, in any large series of people suffering from iridocyclitis, there will be a considerable percentage to whose origin there is no clue, unless the observer happens to be a fanatic. The proportion of unsolved cases is greater among female than among male victims, largely because typical gonococcal iridocyclitis seldom arises in women.

CO-OPERATION BETWEEN DENTAL AND OPHTHALMIC SURGEONS

Theoretically an eye capable of resisting certain toxins entering the circulation from unhealthy teeth might be rendered vulnerable in consequence of trauma. Therefore many ophthalmologists, unless the case is urgent, deliberately refrain from performing an intra-ocular operation until any necessary dental treatment has been completed. Others maintain that this precaution makes no appreciable difference to the prognosis, and some go so far as to say that post-operative complications are rendered more likely by the flood of toxic matter dislodged by dental extraction, and they point out that removal of any considerable number of teeth is often followed by general lowering of a patient's power of resistance. Perhaps the best solution is to treat every case as a separate problem, but certainly it seems a reasonable precaution in all except urgent cases, to postpone intra-ocular surgery pending dental treatment, if gross oral sepsis comes to light. It would also seem wise, in cases requiring multiple tooth-extraction, to arrange for a few weeks' convalescence before the eye operation is performed.

There are many other fields for fruitful co-operation between these two branches of surgery. During the World War of 1939-45 important pieces of research had to be shelved in favour of activities calculated to produce immediate results, and specialised training was perforce curtailed. There is, however, another side to the picture. Under the impact of war, opportunities arose for trying-out new methods of treatment on a large scale, and the maxillo-facial units, of which mention has already been made, enabled ophthalmic and dental surgeons to realise how many of their problems overlap. Now it seems certain that technique will continue to grow more specialised in every branch of medicine and surgery, and all such improvements count as progress. Neverthless they sound a note of warning. Each successive refinement in technique is a potential barrier or path of divergence between one kind of specialist and another, so that we must be vigilant to keep an eye upon the borderline territory—yes, and to maintain a firm *bite* upon joint problems. Long ago Saint Lucia was singled out as the patroness of the eye, and a similar rôle was granted in the realm of dentistry to Saint

Apollonia, but some of the ancient English people looked upon Saint Lucia as the luminary responsible for both sets of organs. Let me conclude with the hope that this primitive belief was of good augury, and that it will serve to emphasise the significance of our eye-teeth.

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CONCENTRATION IN THE AQUEOUS OF VARIOUS SULPHONAMIDES AFTER SYSTEMIC ADMINISTRATION*

BY

ARNOLD SORSBY

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THE earlier experimental studies of Bellows and Chinn (1939 and 1941), Pinkoff (1939), Meyer, Bloch and Chamberlain (1941), Liebman and Newman (1941), and Scheie and Souders (1941), have established that sulphanilamide and sulphapyridine penetrate readily into the interior of the eye on oral administration, whilst sulphathiazole has a poor penetration. The penetration of sulphadiazine was found to be high (Scheie and Souders, 1941; Liebman and Newman, 1941). There do not appear to be any studies on the newer sulphonamides such as sulphamezathine and sulphamerazine. For clinical purposes sulphanilamide and sulphapyridine can be ignored as they are no longer widely used owing to their relative toxicity. In practice the choice to-day is

* Dedicated to Professor J. Meller.

largely limited to sulphadiazine, sulphamerazine, sulphamezathine and sulphathiazole. The present study was undertaken to assess the relative penetration of these sulphonamides into the aqueous.

Animals used. The penetration of sulphadiazine, sulphamerazine and sulphamezathine into the aqueous was determined in rabbits. The penetration of these sulphonamides, as also of sulphanilamide and sulphathiazole, was studied in the rat.

Technique. In the rabbit a dose of 100 mg. per kg. of bodyweight of sulphadiazine, sulphamerazine and sulphamezathine was given intravenously, and the concentration of these different sulphonamides was assessed in the plasma, blood, and aqueous. In the rat a dose of 150 mg. per kg. was given orally. The values recorded are in each case averages of readings in four animals for each time period shown.

CONCENTRATION IN THE AQUEOUS OF THE RAT

Figs. 1-5 show the concentrations obtained in the plasma, blood and primary aqueous from the administration of each of the five sulphonamides studied, sulphanilamide, sulphadiazine,

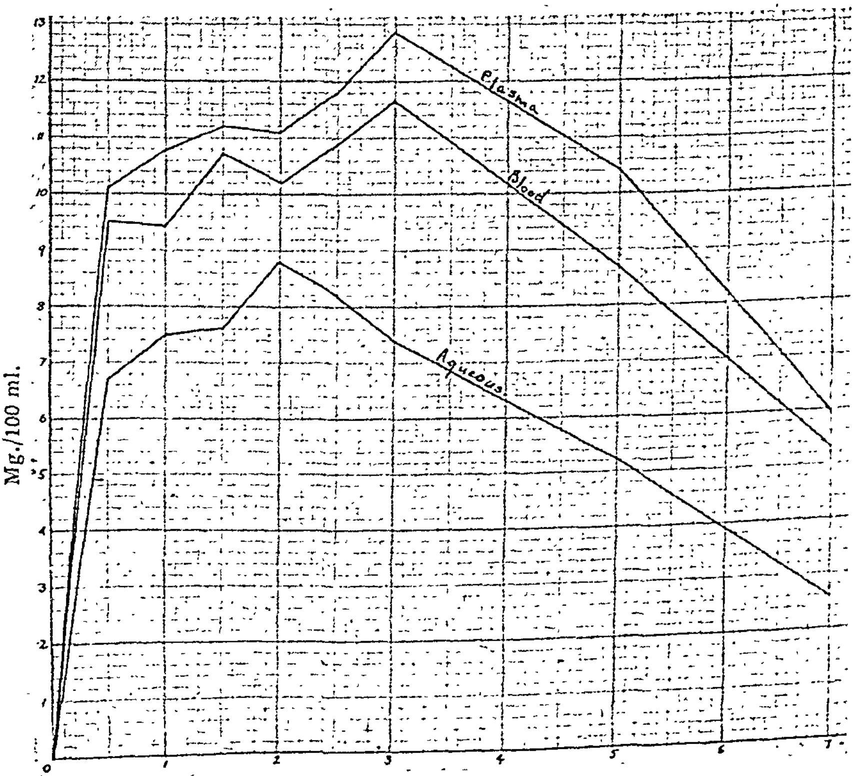

FIG. 1.—Sulphanilamide—150 mg./kg. orally in rats.

sulphamerazine, sulphamezathine and sulphathiazole. Fig. 1 confirms earlier observations that with sulphanilamide high immediate levels are obtained in plasma, blood and aqueous. It will be seen that at 7 hours the aqueous level is still as high as 2·6 mg./100 ml. Fig. 2 shows that sulphadiazine has a rather lower level, whilst Fig. 3 shows a somewhat higher level with

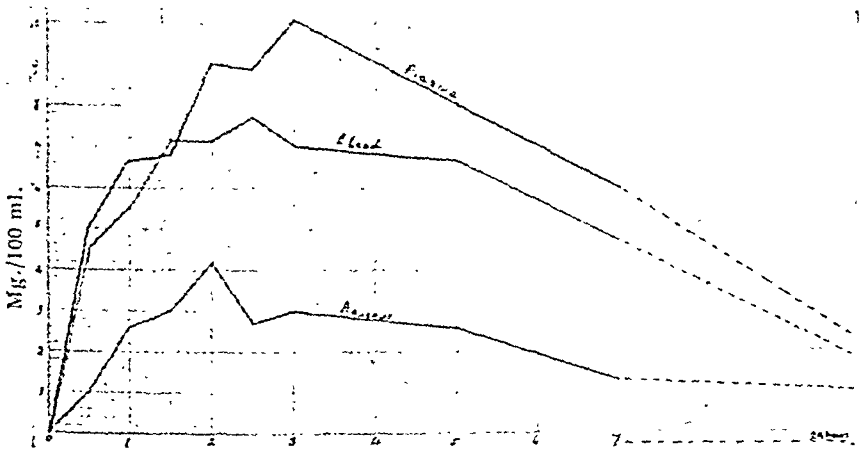

FIG. 2.—Sulphadiazine—150 mg./kg. orally in rats.

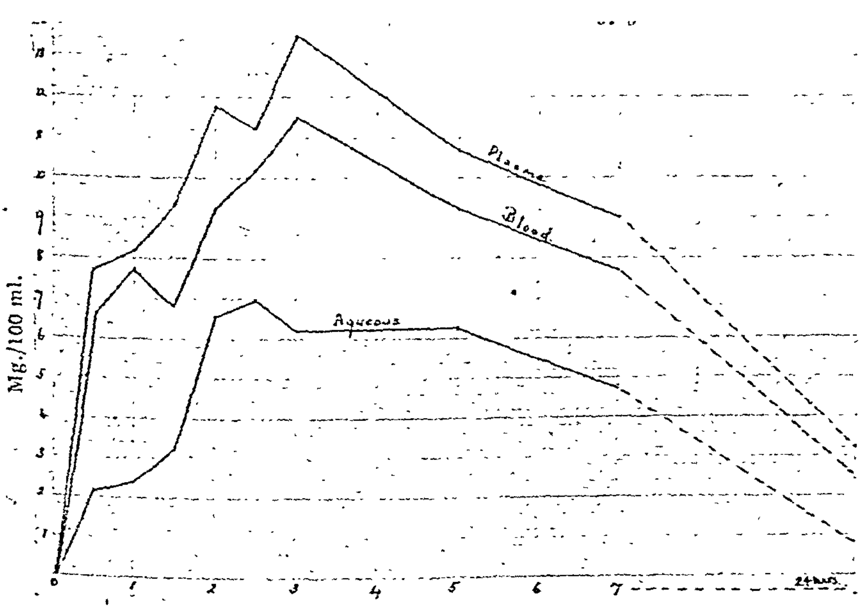

FIG. 3.—Sulphamerazine 150 mg./kg. orally in rats.

sulphamerazine. The levels for sulphamezathine (Fig. 4) are lower than for sulphamerazine and not dissimilar to those for sulphadiazine. Fig. 5 shows a consistently low level for sulphathiazole, with total disappearance of any concentration by

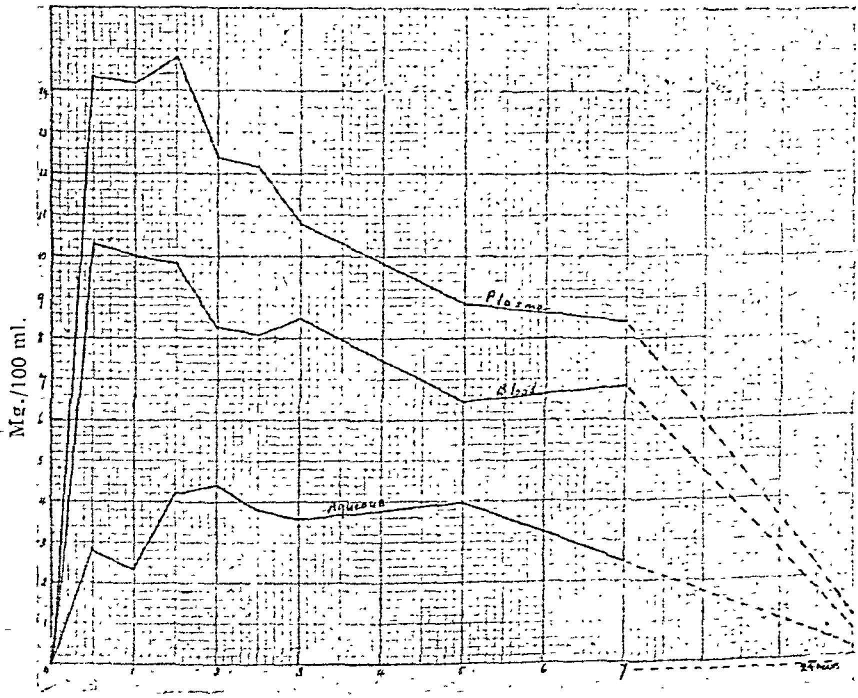

FIG. 4.—Sulphamezathine—150 mg./kg. orally in rats.

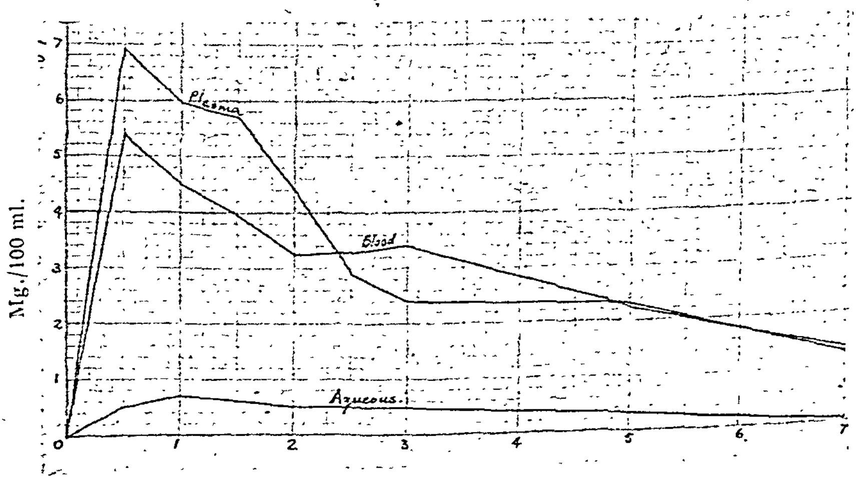

FIG. 5.—Sulphathiazole—150 mg./kg. in rats.

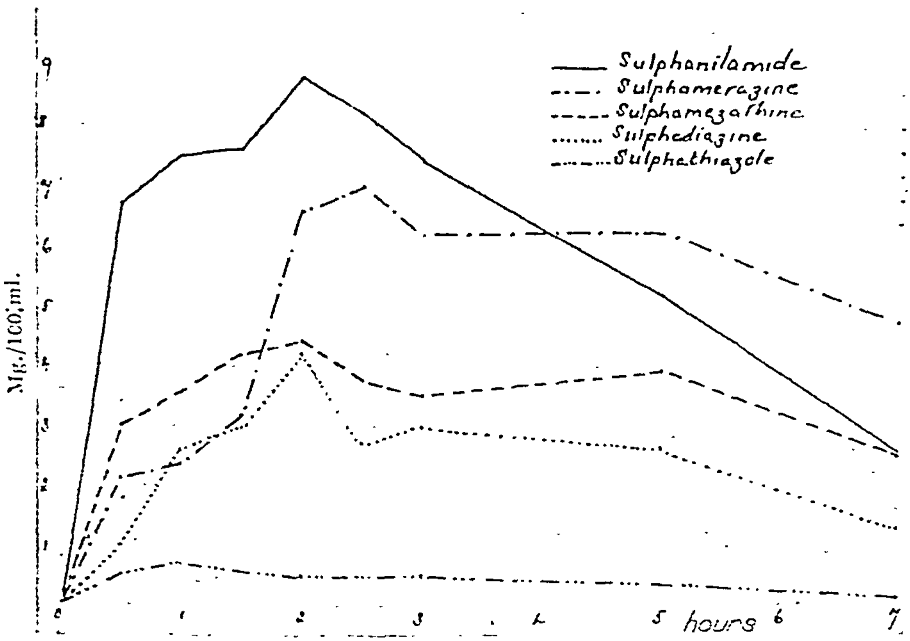

FIG. A.—Sulphonamides—150 mg./kg. orally in rats. Comparison of the aqueous concentration

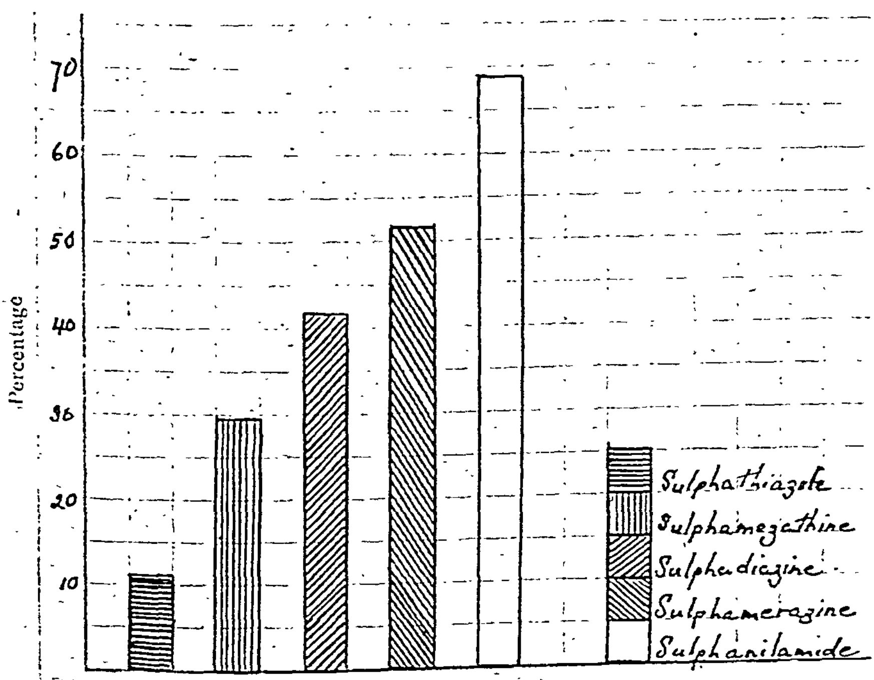

FIG. B.—Sulphonamides—150 mg./kg. in rats.
Highest aqueous concentration as percentage of highest plasma concentration for each of the five sulphonamides.

TABLE I

Comparative levels of concentration of five different sulphonamides in the aqueous and plasma of the rat on oral administration of a single dose of 150 mg. sulphonamide per kg. bodyweight.

Sulphonamide	Aqueous				Plasma		Highest aqueous level as percentage of highest plasma level
	Highest Concentration		Concentration mg/100 ml.		Highest Concentration		
	Quantity	Time	At 7 hours	At 24 hours	Quantity	Time	
Sulphanilamide	8·8 mg/100 ml.	2 hrs.	2·6	—	12·8 mg/100 ml.	3 hrs.	68·8
Sulphadiazine	4·2 ,,	2 ,,	1·3	1·0	10·0 ,,	3 ,,	42·0
Sulphamerazine	7·0 ,,	2½ ,,	4·8	0·8	13·5 ,,	3 ,,	51·9
Sulphamezathine	4·4 ,,	2 ,,	2·5	0·3	14·8 ,,	1½ ,,	29·7
Sulphathiazole	0·7 ,,	1 hr.	0	—	6·9 ,,	½ hr.	10·1

the 7th hour. At 24 hours there is no sulphanilamide at all in the aqueous, whilst the levels for sulphadiazine and sulphamerazine are around 1 mg. per 100 ml., with an even lower reading for sulphamezathine. The absolute aqueous concentrations of these five sulphonamides are contrasted in Fig. A, whilst Fig. B shows the highest aqueous levels as percentages of the highest plasma concentration of each of the five agents. The salient features brought out may be summarised in the table.

It will be seen that on all counts sulphathiazole is the least satisfactory. Of the remaining four agents sulphanilamide and sulphamerazine both reach considerable aqueous levels, 8·8 and 7·0 mg./100 ml. respectively at their peak, (2 hours and 2½ hours respectively), as against 4·2 and 4·4 mg./100 ml. respectively, (both at 2 hours) for sulphadiazine and sulphamezathine. At 7 hours sulphamerazine still has a relatively high level, 4·8 mg./100 ml., whilst sulphamezathine has double the level of sulphadiazine, 2·6 mg./100 ml. against 1·3.

CONCENTRATION IN THE AQUEOUS OF THE RABBIT

In the rabbit the plasma, blood and aqueous values for sulphadiazine, sulphamerazine and sulphamezathine after intravenous injection are shown in Figs. 6-8, and the aqueous values are contrasted in Fig. C. Fig. D shows the highest aqueous levels as percentages of the plasma levels at 30 minutes after injection.

The salient features are shown in the following summary table.

TABLE II

Comparative levels of concentration of three different sulphonamides in the aqueous and plasma of the rabbit on intravenous administration of 100 mg. sulphonamide per kg. bodyweight.

Sulphonamide	Aqueous: Highest Concentration: Quantity	Aqueous: Highest Concentration: Time	Aqueous: Concentration mg/100 ml.: At 3 hrs.	Aqueous: Concentration mg/100 ml.: At 7 hrs.	Highest aqueous level as percentage of plasma level at ½ hour
Sulphadiazine	6·0	1½ hrs.	1·8	0·2	53·6
Sulphamerazine	3·5	½ hr.	1·1	0·2	52·3
Sulphamezathine	5·0	½ ,,	0.6	0·0	61·0

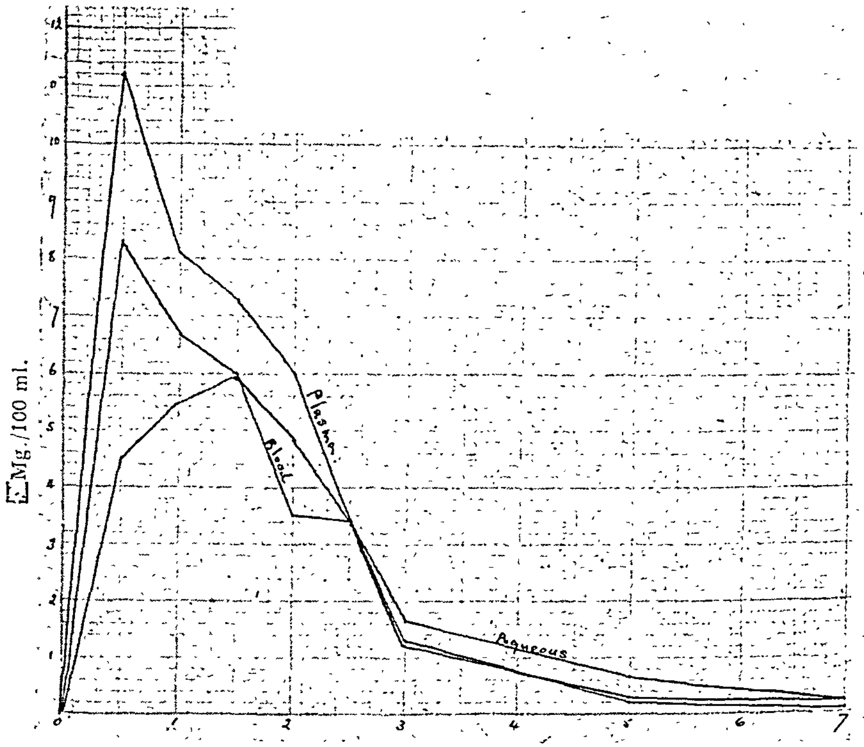

FIG. 6 —Sulphadiazine—100 mg./kg. intravenously in rabbits.

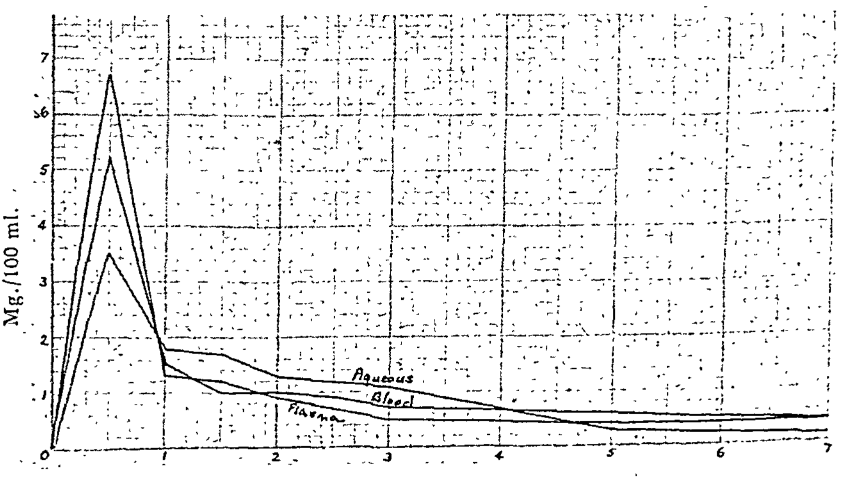

FIG. 7.—Sulphamerazine 100 mg./kg. intravenously in rabbits.

It is seen that the highest absolute aqueous concentration is reached with sulphadiazine, and that sulphamezathine gives a higher level than sulphamerazine. Sulphamezathine appears to be most rapidly eliminated, but it gives the highest ratio of aqueous/plasma concentration.

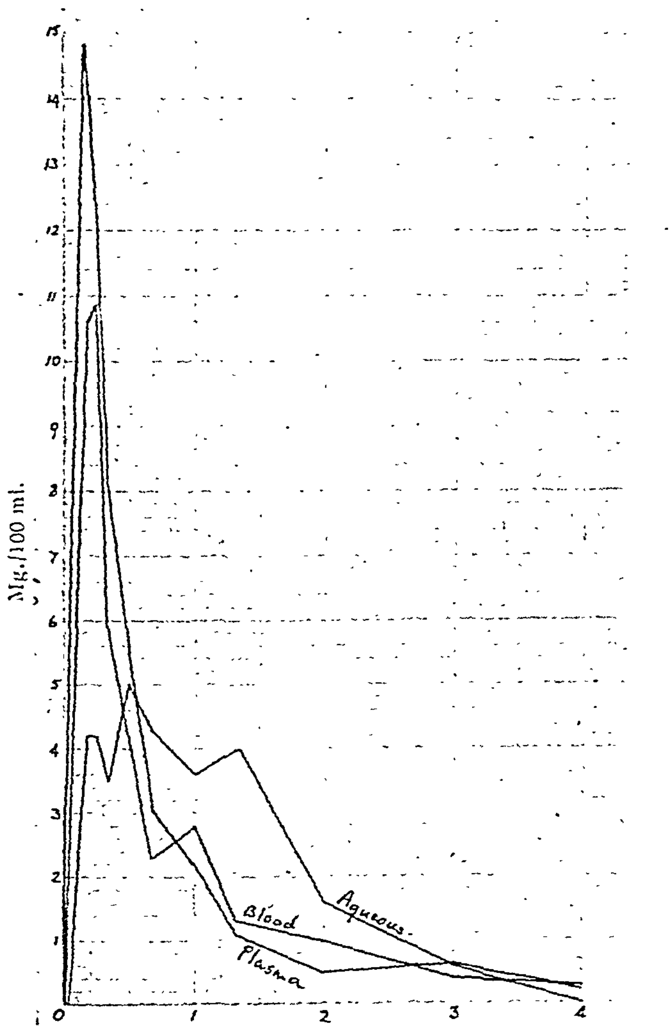

FIG. 8.—Sulphamezathine 100 mg. kg. intravenously in rabbits.

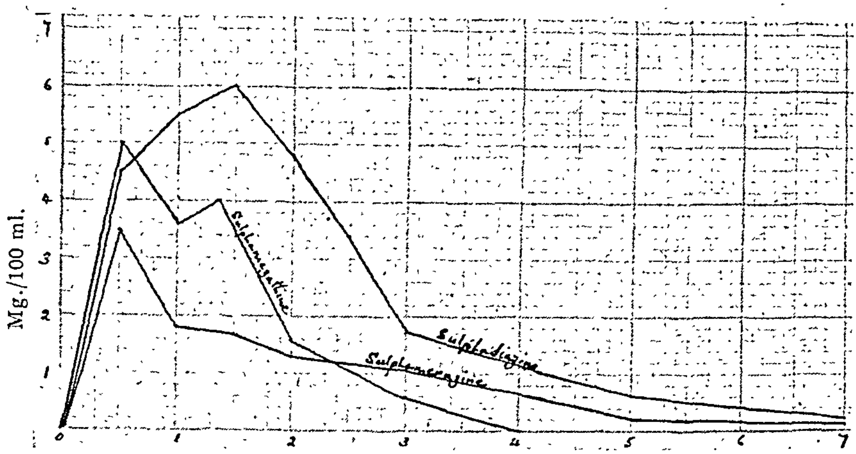

FIG. C.—Sulphonamides—100 mg./kg. intravenously in rabbits. Comparison of the aqueous concentration.

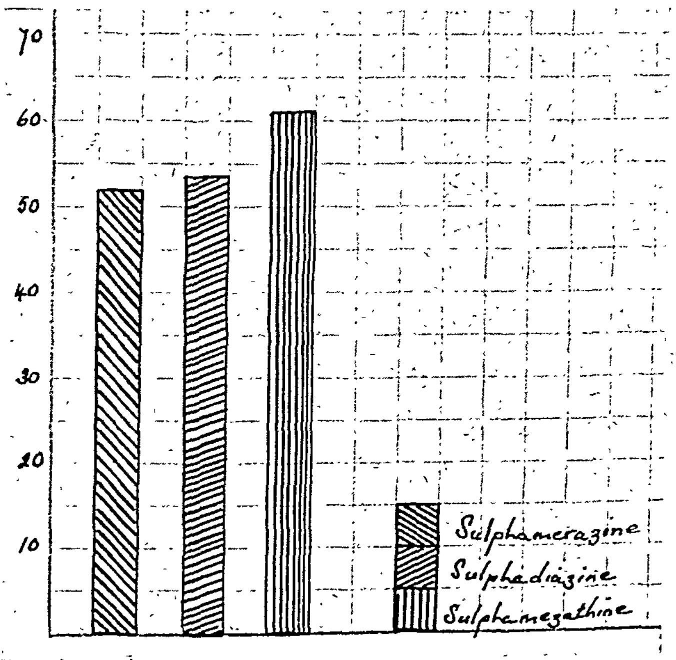

FIG. D.—Sulphonamides—100 mg./kg. intravenously in rabbits.

Highest aqueous concentration as percentage of highest plasma concentration for each of the three sulphonamides.

DISCUSSION

With the reservation that whilst neither absolute values, nor ratios of aqueous concentration to plasma concentration, nor the time factors established in the experimental animal can be applied uncritically to man, the following conclusions are warranted.

(1) *Absolute values in the aqueous.* Sulphathiazole is the least satisfactory. In the rat both sulphanilamide and sulphamerazine give higher values than sulphadiazine and sulphamezathine, but in the rabbit both sulphadiazine and sulphamezathine give higher levels than sulphamerazine.

(2) *Ratio of aqueous concentration to plasma concentration.* Here, too, sulphathiazole is least satisfactory. In the rat both sulphanilamide and sulphamerazine give higher ratios than sulphadiazine and sulphamerazine, but in the rabbit there is no substantial difference between sulphamerazine and sulphadiazine, whilst sulphamezathine gives a higher value than either.

(3) *Rate of excretion from anterior chamber.* In the rat at 7 hours after oral administration the aqueous concentration is nil with sulphathiazole, and 4·8 mg./100 ml. with sulphamerazine. Intermediate and successively diminishing values are recorded with sulphamezathine, sulphanilamide and sulphadiazine. In the rabbit the values at 3 hours after intravenous administration are highest for sulphadiazine, lowest for sulphamezathine and intermediate for sulphamerazine.

Eliminating sulphanilamide from consideration because of its toxicity, the one clear conclusion that emerges is the unsuitability of sulphathiazole for use in intra-ocular infections. Of the remaining three sulphonamides, sulphamezathine appears to be rather better than sulphadiazine, whilst sulphamerazine is clearly superior to sulphamezathine judging by the levels and persistence obtained in the rat—a superiority not apparent in the rabbit.

SUMMARY

1. Sulphonamide concentrations in the aqueous were determined for sulphanilamide, sulphadiazine, sulphamerazine, sulphamezathine and sulphathiazole after oral administration of 150 mgm. per kg. bodyweight in the rat. Similar determinations were carried out for sulphadiazine, sulphamerazine and sulphamezathine administered to the rabbit intravenously in doses of 100 mg. per kg. of bodyweight. Corresponding values were established for blood and plasma.

2. In the rat the highest concentration in the aqueous was given by sulphanilamide, with successively lower readings for

sulphamerazine, sulphamezathine, sulphadiazine and sulphathiazole. As for persistence, as measured by the presence of sulphonamide in the aqueous 7 hours after administration, sulphamerazine gave the highest value with successively decreasing values for sulphamezathine, sulphanilamide, sulphadiazine and sulphathiazole. Assessment of the highest aqueous level as a percentage of the highest plasma level showed the highest value for sulphanilamide, with successively lower values for sulphamerazine, sulphadiazine, sulphamezathine and sulphathiazole.

3. In the rabbit the highest concentration in the aqueous was given by sulphadiazine, with successively lower values for sulphamezathine and sulphamerazine. Sulphadiazine also proved to be the most persistent as assessed by the aqueous concentration at 3 hours. The highest aqueous/plasma ratio was shown by sulphamezathine.

I am greatly indebted to Dr. A. Spinks, of the Research Laboratories. Imperial Chemical Industries Ltd., Manchester, for assistance in carrying out the experiments.

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THE SIGNIFICANCE OF OCULAR COMPLICATIONS FOLLOWING VACCINATION*

BY

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THE occurrence of ocular complications shortly after vaccination, of the secondary or indirect variety, is not new, for it has been reported in ophthalmic literature about twelve times. The observation of a greater number of cases in a period of two months would indicate that these complications should provoke greater interest than they have hitherto received. This secondary type of ocular complication is so named in order to differentiate the accidental vaccinial inoculation produced by first scratching the

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pustule and then touching the eyelid, from the ocular complication which is endogenous and usually part of a post-vaccinial encephalitic phenomenon.

While at Fort Benning, Georgia, in 1945, I observed an interesting case of interstitial keratitis associated with vestibulo-auditory symptoms following vaccinia. This case was similar to four cases reported by David Cogan[4], which introduced a new syndrome of unknown aetiology, namely, non-syphilitic interstitial keratitis associated with vestibulo-auditory symptoms. After studying these cases it appeared that our case was one of the same syndrome, save that the patient's symptoms developed seven days after vaccination. It seemed that this syndrome might be a variety of post-vaccinial encephalitis, since both the fifth and eighth cranial nerves were involved. The syndrome was bilateral, recurrent and reversible. The case report in some detail is as follows:—

The patient was a 30-year-old male who had served in the armed forces for over four years. The onset of acute illness occurred on March 13, 1945, one hour after the noonday meal. The initial symptom was nausea which was followed shortly by retching and then by projectile vomiting. After vomiting had ceased the patient noticed a persistent dull nuchal headache which did not keep him from his work that afternoon, throughout which it remained unchanged. There were no chills, dizziness or fever at this time. The patient slept well that night, but on awakening the next morning he felt dizzy, as though the bed were rotating. This sensation vanished in a few hours, so that he was able to report to work at the usual time. Again, following a frugal noonday meal, the symptoms of the previous day returned, together with an oppressive tightness about the neck. The dizziness recurred, and he returned home, where he spent a comfortable night. On this second day the headache did not recur. When he got up on March 15, the patient was still dizzy and somewhat faint. He was admitted by ambulance to the hospital, where followed a mild bout of retching. The only symptom for the first week was persistent dizziness, more pronounced when the patient stood up. At no time was the temperature abnormal. His past history indicates that the patient has had several mild virus diseases, including several slight attacks of herpes labialis. Mumps, measles, scarlet fever and chicken-pox were all contracted without any serious sequelae. On March 6 the patient was vaccinated with vaccinia virus, and was also given a stimulating dose of triple typhoid. There was no systemic or local reaction to the vaccination or to the typhoid injection, and the incident had been forgotten.

On admission the physical examination was reported as normal. The temperature was 98°, the blood pressure was 114/86, and the pulse rate was 86. There were no neurological signs and no physical findings other than vertigo. The urine examination was negative. A blood count performed upon the day of admission showed a leucocytic count of 11,700 of which 72 per cent. were "polymorphs" and 28 per cent. "lymphocytes." Several subsequent blood counts were performed with an 8,000 to 15,000 leucocytic variation, and maintenance of the above percentage for the differential count. Routine tests for syphilis, undulant fever and tularemia were reported as being negative. Spinal fluid studies were made ten days after the onset of the illness, and were reported as normal. X-rays of both the skull and the chest were negative. Because of the persistence of vertigo without associated symptoms further consultation was sought along otological and neuropsychiatric lines. The neurological examination was negative. The psychiatric examination is summarized in the following paragraph:—"This officer appears to be a passive neurasthenic individual. In the service he failed to gain a commission because of lack of physical performance and leadership of men

in a combat type of duty. He was given a form of work following this failure which was technically and psychologically very acceptable to him. As a result of his work he gained a warrant officer's status which to him was very gratifying. While on leave, he was, without previously being informed, relieved of his command and placed upon an "available" list. He took this in a normal manner consciously, and reacted with "well a soldier is never put." Psychologically, however, this was a serious failure upon his part. With this news there was the threat of combat theatre duty and separation from his wife, upon whom he depended a great deal emotionally. He reacted to the situation in the only manner he is capable of, namely, an acute episode of hysteria. His neurasthenic features have existed for many years and manifested themselves early in his military career. Diagnosis:—psychoneurosis and neurasthenia.

Ear, nose and throat studies were of indeterminate value. Upon rechecking the history it was learned that two years earlier the patient had noticed buzzing in his ears shortly after swimming. This buzzing had only lasted two days. One week after the onset of acute vertigo the patient complained of transient auditory disturbances. He described two distinct kinds: one was of the "cockleshell" variety; the other resembled the hum of an undialled telephone. The otologist reported that the results of his audiometric and labyrinthine studies were unreliable, transitory, indeterminate and contrary to expectation. During the second week the transient auditory symptoms appeared. Ocular manifestations arose about the first of April, being quite mild at the onset. The right eye was first involved. There was no pain and no secretion. There was a mild conjunctival injection and a slight sensitivity to light. After instillation of a mild astringent (zinc sulph. ½ per cent.) the eye appeared to improve, and remained comfortable for about ten days, after which time similar but more severe symptons recurred. Examination at this time disclosed slight aqueous flare, thickening of the cornea, several folds in Descemet's membrane, and many "craters" visible in the zone of specular reflection. There were also several small foci of opacification in the corneal stroma. At various places the limbal vessels were beginning to push into the corneal substance superficially. Under atropine drops locally, and typhoid therapy intravenously, the right eye gradually cleared in about three weeks, but by this time a similar picture had begun to develop in the left eye. Attacks continued to shift from one eye to the other, each attack lasting about one week, and then clearing without any residuum. The attacks were unrelated to any systemic manifestation. The events leading up to the patient's hospitalization, along with the neuro-psychiatric findings and the presence of conjunctival secretion, even when a definite keratitis existed, aroused the suspicion of malingering. The patient was kept under observation, and there was a gradual improvement over many months. In this period there were several recurrences, but eventually all ocular and otologic symptoms subsided.

From this case report it seemed apparent that since ophthalmology deals with fifty per cent. of the cranial nerves, and since post-vaccinal encephalitis is a cranial nerve involvement, the ophthalmologist should be in an excellent position to see cases of post-vaccinial encephalitis at an early stage. Looking upon the eye as a bud from the brain, in whose interior one can deduce events occurring in the brain, particularly as regards vascular structures, it seems that there is further evidence of this ocular localization in complications of post-vaccinial encephalitis. The ophthalmologist may well detect certain vascular phenomena in the eye—for example, in the avascular cornea—and thus solve the problem which for so many years has eluded the clinical investigator seeking to explain the aetiology of post-vaccinial encephalitis. Changes in the optic nerve-head from pressure disturbances, inflammation and congestion, are not the only possibility. Direct

observation of the blood-vessels may be of value when the blood itself is altered, and the importance of the avascular cornea for observation of allergic phenomena cannot be over-emphasized, as shown by the work of Rich and Folis, 1940[9], whose studies of allergic phenomena in such tissues led them to believe that sensitization is due to the capillaries at the corneal limbus, not to corneal tissue *per se*. In animals previously sensitized, serum injected into the cornea produced inflammatory changes at the limbus. If, however, one eye had an artificially vascularized cornea, serum introduced into the cornea of a sensitized animal produced a haemorrhagic area within the corneal stroma itself at the terminus of this acquired vascularization.

A second case which we observed has a bearing upon the experiments of Rich and Folis.

Mr. J.K., age 37 years, was first seen at Camp Lee, Virginia, in the Fall of 1944 because of a severe metaherpetic keratitis in the left eye. This was his third attack. The lesions responded to treatment very slowly, requiring ten weeks of hospitalization before any permanent improvement was effected. Then he was discharged, and returned to duty. He remained free from eye symptoms until two weeks after vaccination in May, 1947, when the left eye became inflamed and painful. Examination revealed an inflamed cornea which was at least doubled in thickness. There was a general greyness over most of the corneal surface. The conjunctiva was intensely injected. There were many folds in Descemet's membrane. The optical section under the narrow beam looked very like a section through a washboard. One vessel ran deeply into the substance of the cornea, starting at nine o'clock. At first the activity seemed limited to the corneal substance just beyond this new vessel. During the acute period the iris could not be seen. Within the substance of the cornea there were several small infiltrates spindle-shaped in cross section. The acute process continued for several weeks, and gradually subsided.

A review of the literature on post-vaccinial encephalitis indicates that the allergic theory cannot be lightly dismissed. Putnam[21], Finley[7], Davidoff[5], Flexner[8], Glanzmann[12] and others believe that post-vaccinial encephalitis is an allergic response, whose incubation period is definitely related to the exanthem. The incubation period may be accelerated, and has been shown to be so in cases of revaccination. The symptoms of post-vaccinial encephalitis usually appear on the eleventh day, but in revaccination they may arise as early as the seventh day. I believe that this incubation period or interval following inoculation is more important than the symptomatology greatly stressed in so many writings. The fact that the patient develops coma, diplopia, nausea, headache, etc., is not nearly so important as the fact that these symptoms appear seven, eight, nine, ten or eleven days after vaccination. Therein lies the most important single finding in a variegated disease which for years has been so baffling.

A review of every autopsy available, both of post-vaccinial encephalitis and of the post-exanthematous encephalitides, made it

clear that one was dealing with the same pathological entity—whether of post-measles, post-pertussis, post-influenzal or the other virus diseases common in childhood. It is not difficult to understand why, for so many years, this problem has been a baffling one. The neuropathological picture in any of these diseases cannot be differentiated by the most competent investigator. On the other hand, when one considers the difficulties encountered in diverse staining techniques of nerve tissue, one can understand the variation in the reports of pathological studies concerning this group of diseases. One striking aspect revealed by this review of post-vaccinial encephalitis is the close relationship between the exanthematous encephalitides and acute multiple sclerosis. There are several ocular observations in support of this relationship. Thus Von Herrenschwand in 1939[24] wrote about ocular complications in post-vaccinial encephalitis. In 1912 he had reported a case of a six-year-old child who developed a post-vaccinial bilateral sixth nerve palsy. In his second report (1939) he listed three new cases, each of which came to autopsy. The patients were all about eight years old. Encephalitis occurred seven to ten days after vaccination, and death followed in two to three weeks. Clinical eye studies were not recorded in these cases, but autopsies including sections of the eye were performed with interesting results. In the first case there was an internal and external hydrocephalus with recent haemorrhage below the dura upon each side of the skull. Both trigeminal nerves and their sheaths were oedematous. The histological picture suggested an allergic response. A bilateral perineuritis of the optic nerve was present. The *post mortem* examination of the second case was most interesting as regards the ocular findings. The histopathological picture was an early retrobulbar neuritis, a condition which rarely comes to autopsy unless death ensues from some other cause. Von Herrenschwand believed that the presence of continuous circular lines of connective tissue within the vein was characteristic of post-vaccinial neuritis, and from this feature one could rule out other forms of encephalitis. Perhaps this concept of retrobulbar neuritis as determined by Von Herrenschwand's histopathological investigation in cases of post-vaccinial encephalitis, and the suggestion that we are dealing with an early allergic response may fit into the picture portrayed by Benedict[2] in his studies upon retrobulbar neuritis. Certainly it is no coincidence that retrobulbar neuritis terminates as multiple sclerosis (Benedict[2]), and that multiple sclerosis resembles the post-vaccinial encephalitis histopathologically (Putnam[21]).

Benedict's work seems further to be substantiated by Adler[1],

in whose series of 100 cases diagnosed as acute encephalitis of all varieties, fifteen per cent. eventually were recognized as multiple sclerosis because of the recurrence of attacks. Putnam has stated that certain types of encephalomyelitis represent the acute stage of a process which we know in its chronic relapsing form as multiple sclerosis. The "sheathing" of retinal blood vessels described by Rucker[22], and the studies of Franklin and Brickner[11] on vasospasm associated with multiple sclerosis appear to be two recent contributions to the study of multiple sclerosis which resemble similar pictures seen in the post-vaccinial ocular syndrome. There have been several cases observed following vaccination in which a process akin to "sheathing" has been seen in the fundus examination. An example of this type of ocular complication is the following: M.H., a 24-year-old male, was in apparently excellent health when he was re-vaccinated against smallpox. On awakening 21 days after vaccination he noted blurred vision more obtrusive in the right than in the left eye. Since he was unable to continue his clerical work, he consulted an ophthalmologist, who found the vision to be 20/50 in the right eye and 20/40 in the left eye. There was a mild bilateral macular oedema and a suggestion of general perivascular bifurcational constriction. The eye became worse in the next three days. Examined on the twenty-fourth post-vaccinial day, vision was 20/70 in each eye. At this time the macular oedema and perivascular sheathing were pronounced. Under vaso-dilators, atropine and rest there was gradual disappearance of the oedema, and return of vision to normal. Aetiological investigation revealed nothing abnormal. Franklin and Brickner in the above-mentioned paper have referred to the recent work of Zeligs'[28] in which macular oedema in young marines producing the characteristic "central serous retinopathy" is attributed to emotional tension with subsequent vasospasm. Franklin and Brickner state that "such tension has a profound and precipitating effect in cases of multiple sclerosis, as has been pointed out by several observers." I have listed five cases of the above syndrome, each coming on within a definite period following vaccination. Two of these cases were reported before the New York Society for Clinical Ophthalmology in May of 1947 and are summarized herein :—

Case 1—(*a*) Mr. M.C., a 38-year-old radio mechanic considered himself to be in good health. He had had no physical ailments for several years. There was no history of allergy either immediate or remote, nor of vasoneurosis, nervous tension nor other features associated with vasospasm. The patient did not smoke. On awakening three days after being vaccinated, he observed in front of his left eye a spot which was more noticeable when he gazed upon a white background.

Examination revealed a characteristic central serous retinopathic lesion. Physical examination including blood pressure studies were normal. The lesion cleared completely in three weeks. There was a central scotoma.

Case 2—(b) J.G., male jeweller aged 38 years, developed a spot before his left eye ten days after vaccination. The vision was only slightly impaired, so that he paid little attention to this impediment except when he attempted to use his jeweller's loupe. Then he found that he could not see an object unless he gazed at it eccentrically. When examined three weeks after vaccination, he was found to have a typical central serous retinitis, which cleared in three weeks. This patient had a mild hypertension. He has been under observation for the past twelve years and has hitherto never had any similar ocular condition.

The most dramatic cases in the post-vaccinial ocular syndrome are those of central serous retinopathy, for here the eye grounds reflect the process going on within the brain. Since post-vaccinial encephalitis has been shown to be limited to the vascular structures, and since central serous retinopathy is a condition in which the tiny macular twigs are involved with passage of fluid into the macula, it seems that in this region one can obtain a clue to certain phenomena arising in the brain. Since this area is vulnerable, the patient too will early be aware of involvement.

The classification of multiple sclerosis within the demyelinating diseases, the vascular distribution, the recognition of an hyper-allergic theory to account for the demyelinating diseases, and the unification of the pathology of the demyelinating diseases (Ferraro[6]) would seem to express a further relationship between post-vaccinial encephalitis and multiple sclerosis. Another case which shows at least a questionable relationship to multiple sclerosis is the following: L.D., adult male age 39, was re-vaccinated in May, 1947. Ten days after vaccination he developed an unsteadiness and a slight swaying to his left side. On the fourteenth day a small central scotoma was present in the right eye. He was found also to have an acute labyrinthitis. Symptoms cleared rapidly in four weeks. Upon neurological consultation he was advised that he might be suffering from acute multiple sclerosis.

In a recent experimental study Morrison[19] has produced encephalomyelitis in animals through the use of homologous antigen. He has speculated upon the possibility of a lipoid antigen resulting from demyelination which could produce such conditions as multiple sclerosis and other demyelinating diseases. His studies substantiate the work of Putnam and of Ferraro, who have repeatedly maintained that the type of lesion one sees in the demyelinating diseases depends to some extent at least on the age of the pathological process. Morrison emphasizes the similarity which exists between the demyelinating diseases and the pathological picture in his experimental encephalomyelitis, which reaction is based upon an immunological response.

Autopsy displayed definite arterial occlusion in some of the animals—a controversial point mentioned by Greenfield[13] and Grinker[29]. If medullation is of great importance in this immunological study, perhaps careful observation could be made upon patients who have medullated optic nerves visible ophthalmoscopically, and upon animals with a normal medullation in the fundi.

During the recent episode of mass vaccination in and about New York City, I observed many vaccinated patients and have had several physicians inform me of various complications following vaccination. There is no doubt that a great many symptoms which follow vaccination are "flare-ups" of dormant conditions. This apparent "light-up" of a so-called dormant condition was the most frequently observed of the ocular complications. Usually there was a healed choroidal lesion which appeared to spring into activity after vaccination. Variation in the onset of the symptoms can be explained by the location of the lesion, especially in respect of its proximity to the macula, and by the degree of exudation. The following cases exemplify this variety of ocular complication :—

Case 1—Miss P., age 23 years, was vaccinated on May 18 in routine fashion. On May 30 she noticed in front of her left eye several large opacities, which became much more pronounced in the bright sunlight, or when she looked at a white background. At first there was only a slight blur, but within three days vision was reduced to counting of fingers. The patient was admitted to the Newark Eye and Ear Infirmary, where all routine studies proved to be negative. These included Wassermann test, urine, Mantoux (1:1,000,000 to 1:10,000 dilution), sinus studies and chest X-ray. Past history revealed chicken-pox, measles and whooping cough, all before the age of five years and all mild in character. There were no complications of these illnesses. The patient had never had any serious diseases and this hospitalization was her first. There was no family history of allergy and the patient had never had any indications of allergic reactions. She was first vaccinated at the age of one, with a normal response. Examination of this girl's eyes disclosed vision of fingers only in the left eye. The pupil was widely dilated; there were many large scattered precipitates on the back of the cornea. The vitreous contained many large greyish opacities, some globular in shape, others resembling large strands. These vitreous opacities were especially thick in the region of, or just anterior to, a large yellowish grey choroiditic patch about three disc-diameters in size. This exudate was quite recent, with edges still not healed and still non-pigmented. Although it was difficult to see through the turbid vitreous, particularly in this region, yet this lesion could be seen just a little beyond an old upper nasal choroiditic patch heavily pigmented and completely healed. The disc appeared normal, although it could not be seen clearly.

Case 2—Mrs. R., age 29 years, was moderately myopic. She had had annual refractions by a well-known ophthalmologist in New York City. Vision had always been normal with her glasses. Physical examination performed after the birth of her second child and three months before the onset of her present eye complaint indicated that there were no abnormalities. About twenty days after an uneventful re-vaccination the patient complained of small spots in front of her left eye. These gradually became more pronounced, leading to further visual obscuration. In about three days the vision was reduced to fingers at four feet.

At the initial examination the left eye was seen to have a severe choroido-retinitis with many large and small corneal precipitates, a turbid vitreous and a large choroiditic patch of recent origin and extremely exudative, in the upper nasal

quadrant. A small haemorrhage was adjacent. Near this new lesion were several smaller old, pigmented choroiditic patches all crowded along the path of the same blood-vessel. Under atropine, compresses, vaso-dilators and rest no appreciable improvement was noted in the next few weeks. The systemic investigation showed no aetiological factor, the following laboratory studies being reported upon as within normal limits: (1) Blood Count, (2) Blood sedimentation rate, (3) Blood chemistry, (4) Urinalysis, (5) Mantoux test 1:1,000 dilution, (6) Wassermann and Kahn, (7) X-ray of chest.

This group of cases illustrating a "light-up" of previously existing conditions need not necessarily be restricted to the eye. During the period of vaccination referred to in the above paragraph, complications following vaccination were seen in all of the specialities. The symptomatology in these specialities has been as variegated as are the symptoms and signs in post-vaccinial encephalitis, and, as in post-vaccinial encephalitis, this variegation should be considered of importance. As in the ophthalmic complications, the important factor is the appearance of symptoms at a specific time interval, namely, seven to twelve days. Thus the appearance of complications elsewhere in the body after the same interval should be regarded with significance. If one only remembers that the patient has been vaccinated, and seven days later he blossoms forth with an ocular complication, then that ocular complication is a product of the vaccination. The nature of the ocular complication is of no importance, from the aetiological point of view. This same principle applies to diseases of other organs.

As mentioned previously, it has been shown that the pathological picture of post-vaccinial encephalitis and the encephalitis of the acute exanthamata are identical. Krieder[15], in experiments and in autopsy studies in measles, has shown a perivascular lesion consisting of a thrombus formation, which explains the nature of the lesion. The participation of the central nervous system in uncomplicated measles is almost constant. The cerebral symptoms of measles, such as the changing uneasy capricious disposition, etc., are seldom considered neurologically. A meningo-encephalitic reaction is frequently seen, but these symptoms vanish very rapidly and are only lightly regarded. Wohlwill[26] has uncovered many lesions of the central nervous system, although encephalitic symptoms were masked during the course of the measles pneumonia. These changes were found at autopsy studies on patients who died of measles pneumonia. It has also been shown that in many cases of post-vaccinial encephalitis the lungs showed bronchial pneumonia of a type similar to that of the measles pneumonia. Parker Heath[14], in reporting upon a case of measles encephalitis, described an ophthalmoscopic picture resembling embolism of the central retinal artery. Because of the significance of this case I am repeating the report in some detail :—

Clinical History.—J.P., a boy of Italian parentage, aged 6 years, had developed measles eleven days before admission. There was a rash, and then convalescence. Blindness developed on the eleventh day after the onset of measles.

Eye Examination.—Ophthalmoscopic examination showed in the right eye a distinct pallor of the nerve head, and a loss of capillary colour, without loss of substance. The most extraordinary picture was seen in the arteries, which were reduced to threads, and were carrying little or no blood. The veins were dark in colour, and reduced in calibre throughout, but relative to the arteries were engorged. The entire retina showed loss of transparency not associated with haemorrhage or exudation. The foveal reflex appeared a deep red, somewhat diffuse, through a more exaggerated overlying non-transparent retina. The left eye presented essentially the same picture. Appearances resembled bilateral embolism of the central arteries. On the seventh day the patient's eyes responded to light stimuli for a short interval. On the tenth day the child suddenly announced that he could see. The fundi showed more filling of the arteries.

Since the pathology of post-measles and post-vaccinial encephalitis have been shown to be identical, it may be assumed that the histopathological picture found in Von Herrenschwand's second case could possibly produce a variation of the fundus picture seen in Heath's case. Heath's patient revealed an eye condition which was bilateral, oedematous, transitory, reversible and in several other features characteristic of allergy. The fundus picture may have been modified by the pressure exerted by fluid in the tissue spaces. The arterial thinning was related to this extra-arterial pressure, whereas the intra-arterial pressure likewise was unusually low, since the systemic diastolic blood pressure was reported as 40 or less.

Heath, in his statement, "It is very unlikely that an opportunity will ever arise for an anatomical study of a similar case," probably would be very interested in the *post mortem* report of Von Herrenschwand's case number two. It appears that, although Heath does not claim an allergic basis for this case report, yet the stressing of localized oedema as the dominant sign points toward such a concept. Furthermore, it would appear that the acute retinal oedema and other vascular changes in the retina in Heath's case, and the retrobulbar picture in Von Herrenschwand's case may be similar in nature to the acute perivascular pathology of encephalitis, if we make proper anatomical allowances. The similarity of the ocular picture shown above lends more significance to many transitory ocular symptoms casually mentioned in measles encephalomyelitis. These symptoms should be considered more gravely since Ford[10] has shown that recovery from measles encephalomyelitis is not nearly as complete as we have believed, and that sequels may arise several years later.

It is the purpose of this paper to show that ocular complications developing within a specific period after vaccination are part of a post-vaccinial ocular syndrome. That such a relationship may

exist in other organs is also hinted at. It would seem, therefore, to be worth while to investigate the state of the host a little more intently before performing vaccination.

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THE TREATMENT OF HYPOPYON ULCER OF THE CORNEA

BY

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THE problem of the infected corneal ulcer in miners has for many years been a serious one in Edinburgh and has been a cause of considerable loss of vision and working capacity. About forty thousand miners are employed in the Lothians and Fife, and the great majority of the eye injuries which occur among them are treated in the Eye Department of the Royal Infirmary. For

many years the number of cases of the so-called "hypopyon ulcer" did not vary much, the average number of admissions per year to the writer's department, the charge of which he assumed in 1932, being about seventy-five. This figure represents about one half of the total number, as the Eye Department is a double one. Under the term "hypopyon ulcer" are included all corneal abrasions which show infiltration at the site of the injury with an inflammatory reaction, whether actual hypopyon is present or not. Two-thirds of the cases were miners, the remaining third consisting of workmen from other occupations with, in addition, a small senile group. Many of the cases did badly in spite of the employment of all forms of treatment then in use. In 1931 Dr. J. R. Paterson had read a paper at the Annual Congress of the Ophthalmological Society of the United Kingdom in which he reviewed 223 cases of traumatic infected corneal ulcer in miners, 182 of which had been treated in the Royal Infirmary. He used the records of cases that had been examined by his father, the late Dr. J. V. Paterson, in connection with claims for compensation. Of the total number, eighteen eyes were lost and only thirty-three retained vision of over 6/12. In over fifty per cent., vision was reduced to less than 6/60. The average stay in hospital was 29·4 days. These were deplorable results, and when, in 1935, the W. H. Ross Foundation for the study of Prevention of Blindness was founded under the guidance of Dr. A. H. H. Sinclair, it was decided to try to improve matters, and work on the problem was begun in 1937. The bacteriological aspects of the problem were investigated by A. J. Rhodes working under Professor Mackie of the Bacteriology Department, but, although much valuable information was obtained, this work gave no help with regard to prognosis and treatment.

In 1939 experimental work on animals was begun by J. M. Robson and G. I. Scott, working under Professor A. J. Clark of the Pharmacology Department, and the results of their research suggested that one of the soluble sulphonamides, sodium sulphacetamide, which is very soluble and non-irritating, should be given a thorough clinical trial both in prevention and therapy. Colonel R. M. Dickson, the Director of the Ross Foundation, undertook to arrange for the preparation to be introduced as a first-aid treatment at the pit-head and in the ambulance-room, and the Ophthalmic Staff of the Royal Infirmary readily agreed to undertake the necessary clinical trials. The results of this work are embodied in a number of papers which have been collected in a volume recently published by the University of London Press entitled "The W. H. Ross Foundation (Scotland) for the study of prevention of blindness." To many ophthalmic surgeons interested in the subject this volume may not, however, be readily accessible, and a short article describing the progress made seems desirable.

With the willing help of the colliery officials the first-aid treatment in the ambulance-room at the pit-head has been reorganised, and the danger of the neglect of apparently trivial eye injuries is now well understood by the officials and the miners themselves. When an eye injury is reported, sodium sulphacetamide in 10 per cent. solution is used as drops, and the miner is directed to continue to attend until danger of the development of serious trouble seems over. Any doubtful case is referred to his own doctor.

It has been the practice for many years to admit all cases of corneal abrasion coming to the Infirmary if they show evidence of even slight infection. These cases are all potential "hypopyon ulcers" and experience has proved the great danger of relying on out-patient treatment. From 1942 till March 1947 when the writer relinquished his charge, sodium sulphacetamide was used in routine treatment and almost entirely replaced other drugs. After penicillin came into general use it was given to supplement sodium sulphacetamide, but only in the now rarely occurring obstinate cases. More extensive use of it was made by Dr. C. W. Graham, who is in charge of the sister department, and his conclusions are given on page 20 of the Ross Foundation volume mentioned above. Sodium sulphacetamide was first used in 30 per cent. solution with considerable success. Dr. H. M. Traquair suggested its use as a solid powder, and, as this proved non-irritating and most efficacious, the writer decided on the following scheme of treatment which is still the standard routine in the hands of his successor, Dr. J. R. Paterson. Atropine is given in the usual way two or three times a day, and the conjunctival sac is kept free from secretion by means of a simple lotion. Sodium sulphacetamide powder is applied by the sister-in-charge a number of times a day, even two-hourly if necessary, and during the night as well in severe cases. After lightly cocainising the eye she heaps some of the powder on the surface of the ulcer, using a small spoon or some other convenient instrument, and holds the lids apart until the powder has dissolved. The number of applications is diminished as improvement takes place, and in the end drops are substituted. The patient is not discharged until danger of further spread of the ulceration has ceased, and when he goes home he is directed to use atropine and sodium sulphacetamide drops during the remainder of his convalescence. Any other form of treatment is now rarely necessary, cauterisation, paracentesis, Saemisch section etc., being seldom indicated.

Since 1942 only two eyes have been lost, one case being a shepherd in a poor state of health, and the other an elderly woman. In 1946, which may be taken as typical of the present position, the last complete year of the writer's charge, thirty cases were admitted, twenty-one being miners. Six were from other occupations and three were

senile cases. Of the twenty-one miners only three spent more than three weeks in hospital, and eight were in the ward for less than ten days. As a follow-up system in the case of miners who have returned to work is difficult to operate, there are records of vision in most cases only on their discharge. Four had vision of less than 6/60, six of 6/36 or better, and nine of 6/18 or better. In two cases there was no record. No miner's eye has been lost since 1942, as compared with the ten per cent. lost in the series reviewed in 1931.

It will be seen that during the last six years a great improvement has been brought about. In fact the method of treatment that has been adopted has altered the whole outlook with regard to hypopyon ulcers. A great deal of visual loss has been prevented, and the freeing of hospital beds that would otherwise have been occupied for long periods has been a great gain. It is possible that improvement in sanitation and working conditions in the pits has played its part, but the way in which the miners live has not greatly changed. Any alteration in the varieties of organisms that infect the cornea, or in their virulence, is improbable. It will be noted that the number of cases from other occupations has diminished also, and in this connection it must be borne in mind that the same first-aid treatment as at the collieries is now used in many works and factories of the area served by the Royal Infirmary. The newer drugs too are used by the practitioner in his surgery, and in the treatment of most corneal abrasions in the hospital out-patient department, whether there is evidence of infection or not. The fact, too, that both practitioner and workmen are more alive to the dangers of slight injuries brings cases to hospital earlier than in past years. When all these points have been taken into account it remains true that we have now a simple and convenient method of treatment which makes success in dealing with the ordinary typical case of hypopyon ulcer practically certain. These cases are no longer regarded with the former dismay and apprehension. A few still do badly — those in older people, those whose admission has been delayed, those in which a deep infection of the cornea through a small puncture has taken place, and a few for no apparent reason. It has been found that, if the sodium sulphacetamide treatment fails to produce early and rapid improvement, penicillin and other forms of treatment are rarely of much more help.

I am indebted to Dr. A. H. H. Sinclair, Colonel R. M Dickson, Dr. H. M. Traquair and the members of the Staff of the Eye Department of the Royal Infirmary for help in the preparation of this paper.

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MODERN VIEWS OF SURGERY OF THE CORNEA*

BY

Professor M. SOBHY BEY

CAIRO

THE aim of this communication is to summarize briefly the present trends in corneal surgery, noting some of my own ideas and preferences, rather than to bring to your notice any particular item or procedure with which you are not already familiar.

For instance, you all know, but it is worth reiterating that, for a foreign body embedded deep in the stroma of the cornea, a keratome should be introduced behind it in the anterior chamber before cutting down on the foreign body from the surface; this is in order to offer counter-pressure from behind, and to prevent the foreign body being pushed into the anterior chamber.

Ulcers of the cornea, whether primary or complicating ophthalmias, are nowadays generally treated by the anti-biotic drugs. The latter are used locally either in the form of solutions for frequent instillations, or in the form of pastes as ointments, or in strong solutions mixed with adrenaline to be used as subconjunctival injections (Sorsby) or in the treatment by ionisation (Sallmann). These methods can be used in combination with each other, and many of the drugs in use can be mixed together in one powder (sulphadrugs+penicillin+streptomycin). The systemic treatment *per os* or by parenteral injections is, as a rule, added to the above.

If in a certain case the anti-biotic treatment is not efficacious, then pasteurization of the base and edge of the ulcer can be carried out by a thermophore regulated by a thermometer at 158° F. (Shahan). For those who have a pyrometric electrode for use in detachment of the retina, I recommend that this be used in place of the thermophore for carrying out the pasteurization, taking care to shorten the time of its application, because diathermy is more penetrating than the ordinary heat.

In ulcus corneae, it is always an advantage to lower the intraocular pressure even if this is within the normal limits; this ensures better nourishment to the cornea, and that is why repeated paracentesis is of great help in intractable cases.

In hypopyon ulcers, Saemisch advised his corneal section at the base of the ulcer from edge to edge. On the same principle, Sondermann prefers trephining the base of the ulcer using an Elliot's trephine for the purpose. Lindner recommends Elliot's

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operation of sclero-corneal trephining in order to avoid perforation of the ulcer itself, with its unfavourable sequelae of anterior synechia and prolapse of the iris. Nowadays keratoplasty has proved to be successful in those cases of corneal ulceration which do not respond to ordinary treatment; by means of this operation the infected tissue surrounding the ulcer is removed by the corneal trephine, and the disc is replaced by another taken from a donor or a cadaver. Superficial or lamellar keratoplasty has also given good results when done at the place of the ulcer or to the side of it (Filatoff).

Partial staphyloma can be excised by an elliptical incision, the lips of which are stitched. This may be done at the same time as an anti-glaucomatous iridectomy or at a subsequent operation.

Total staphyloma, when excised, leaves a satisfactory movable stump which is to be preferred to that obtained by grafts of cartilage, plastic or other materials implanted after the excision of the globe. When applied in suitable cases, and if properly done, no danger is to be expected. A contact glass, the optical part of which bears a design of an iris similar to that of the fellow eye, will be a good camouflage to an eye the cornea of which looks bad or is disfigured.

Keratectomy becomes inevitable in cases of symblepharon covering the cornea (see the work of Castroviejo and others). Partial or total superficial lamellar keratoplasty in the hands of experienced operators must take the place of total keratectomy (Paufique and Sourdille).

For recurring pterygium a buccal mucous membrane graft should be placed at the edge of the limbus and concentric to it, with or without a lamellar corneal graft shaped to cover the denuded corneal area obtained after dissecting the head of the pterygium.

Conical cornea, if not suited to contact glasses, has to be handled surgically. Cauterisation, perforation and cicatrization of the apex of the cone of the cornea, previously recommended, is no longer an operative necessity. Perforating keratoplasty is the best solution if agreed upon between patient and surgeon. Lindner advocates a new procedure: he introduces a Bowman's needle into the anterior chamber and with it scarifies Descemet's membrane in the weakest and thinnest area of the cornea at the apex of the cone. As a result, the stroma corresponding to the scarified area imbibes fluid from the aqueous and becomes thickened. Later this is followed by cicatrisation and some degree of flattening.

In incised wounds or traumatic ruptures of the cornea, if complicated by incarceration of iris tissue, the prolapsed part should

be pulled out and cut, and the iris reposed after cleaning the wound. The same applies to wounds of the sclera near the limbus. Corneal and scleral wounds should be stitched edge to edge, using very fine silk thread (No. 0000, supplied by N. Dugast, Paris) and small extra sharp needles (supplied by Grieshaber of Schaffhausen, Switzerland). Perfect coaptation of the edges of corneal wounds is a necessity; otherwise irregular astigmatism will result, and there is no satisfactory means of correcting it. If the surgeon is not in possession of the above instruments, he will have to resort to complete or partial conjunctival covering, according to the extent of the wound. The following is a useful modification of the conjunctivo-plastic flap: a rectangular flap of conjunctiva is prepared, starting its dissection as high as possible in the upper fornix; the flap is then turned down like an apron, with its epithelial surface in contact with the anterior surface of the cornea; with any form of flap and without corneal sutures, the accurate coaptation of the edges of the wound is largely a matter of luck.

When there is actual loss of corneal tissue as a result of lacerated wounds, conjunctivo-plasty must be used, and in such cases the raw surface of the flap should be applied to the cornea.

Barraquer was kind enough to supply me with exceedingly fine silk threads that can hardly be seen (crude silk), and they are advisable for corneal sutures. In the Vienna clinics (*e.g.*, Lindner's), Japanese or Chinese hair is employed; horse-hair can also be used. Extra care should be taken in sterilizing the hairs in the autoclave.

If prolapse of the iris takes place after perforation of a corneal ulcer, and conservative treatment with mydriatics does not succeed in breaking the anterior synechia, the patient must be prepared for surgical intervention. When the perforation and prolapse are of small size, a conical probe is used to push the iris back from its adhesions to the perforated part in the cornea; if this manoeuvre proves unsuccessful, subconjunctival injection of adrenaline and atropine might break down the adhesion; if this also fails, the prolapsed piece of iris is caught by an iris hook or by a fine iris forceps, pulled out and cut with scissors; this is followed by reposition of iris and by subconjunctival injection of adrenaline and atropine to prevent further formation of an anterior synechia. Should the corneal perforation be big enough to allow the entry of an iris repositor, it is recommended that the operator should use this repositor instead of the conical probe. In any case, care must be taken not to injure the lens.

Fistula of the cornea is usually associated with secondary glaucoma although the continuous loss of aqueous, of course,

gives rise to hypotony. Binocular bandage, rest in bed, and miotics, should be given a trial before a decompression operation is done. It is usual in such cases to perform a broad iridectomy. The latter, however, gives rise to much spherical aberration and astigmatism while, if you add to this the fact that the central or paracentral part of the cornea is occupied by an adherent leucoma, it is easy to understand why the resultant vision is usually poor. A better procedure is that recommended, many decades ago, in the Vienna school: a corneal trephining (the size of the trephine depends upon the extent of the anterior synechia) is made so as to include the fistula in the disc, and the trephine is applied obliquely in such a way as to obtain an incomplete disc with a trap-door hinge (Sachs). The door should give direct access to the part of the iris pulled and stretched by the anterior synechia. The latter is caught by a forceps or a blunt iris hook and cut, the corneal disc being pulled forwards during this manoeuvre. The hinged disc is then reposed. and binocular bandaging. as a rule, is enough to ensure closure and cicatrization of the corneal wound made by the trephine.

In the modern conception of keratoplasty, the corneal trephine is applied vertically, the whole disc is cut away and replaced by another taken from a donor's eye. Anyhow, the operator can either free the anterior synechia and do the keratoplasty at a subsequent sitting, or perform both at the same sitting.

If my Egyptian colleagues wish to practise keratoplasty, I advise them to do their best to combat the anterior synechia so often met with in this country as a result of the innumerable external diseases and ophthalmias. The anterior synechia is the enemy of the transplant, which will never remain clear if connected with the iris tissue.

Many operators have proved that a successful keratoplasty is far superior to visual iridectomy in central leucomata, even if these leucomata are tattooed.

SUMMARY

At present, anti-biotic treatment applied locally or systemically against ophthalmia has made ulceration of cornea a rarity, and when ulcers do occur they are less liable to perforate. Sclero-corneal trephining, as recommended by Lindner, obviates iris prolapse and adherent leucomata in hypopyon ulcers when perforation is imminent. If the iris prolapses, it should be freed from the cornea, pulled out and cut, if the defect in the stroma of the cornea is of moderate size. The deficiency in the cornea can be replaced by conjunctivoplasty and keratoplasty. The

same procedure is to be adopted for wounds of the cornea, the edges of which should be sutured in accurate apposition in order to avoid subsequent irregular astigmatism. When an adherent leucoma is already present, one should proceed as recommended by Sachs of Vienna, *i.e.*, the cornea in front of the adherent iris is incised with a corneal trephine applied obliquely, so as to cut an incomplete disc attached by a pedicle; the iris is then freed from the cornea by pulling on the adherent part and cutting it; the corneal disc is finally reposed with or without the insertion of sutures. A deep perforating keratoplasty may be necessary later for optical reasons. When Lindner's method does not bring attenuation of the ectasia of conical cornea, deep perforating keratoplasty is applied. Ectatic irregularity on the anterior surface of the cornea should be corrected by partial or total staphylectomy, and a better cosmetic effect is obtained by fitting a contact glass (Jena glass—Zeiss) on the corneal part of which an appropriate iris pattern and pupil are drawn. This is preferable to excision of the globe and the wearing of an artificial eye.

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INJECTION OF THE RETINAL VASCULAR SYSTEM IN ENUCLEATED EYES*

BY

I. C. MICHAELSON and H. F. STEEDMAN†

GLASGOW

So far as we know, studies of the injected retinal vascular system in man and animals have been dependent on injections given into the heart, internal carotid or ophthalmic arteries when the globe is *in situ*. This method does not permit the study of the injected retinae of eyes enucleated because of pathological conditions. To overcome this the following technique has been devised whereby an injection of the retinal capillaries of the freshly enucleated eye may be obtained.

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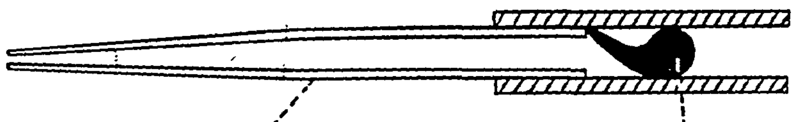
† From the Departments of Ophthalmology and Zoology, University of Glasgow.

Material and apparatus

A wash bottle or related container is used to hold the injection medium. It is supplied with air from a hand or foot pump, and is much more satisfactory than a syringe. The use of such a pressure bottle enables injections to be made in comfort and without an assistant. A Drechsel gas washing bottle is convenient. A mercury manometer should be incorporated in the system.

The outflow tube of the bottle is connected by rubber tubing to a cannula made by drawing out glass tubing.

An essential device in the apparatus is a glass valve in rubber tubing touching the cannula as shown in the following diagram.



Both the cannula and the valve are held between the finger and thumb so that when the cannula is inserted into the central retinal artery pressure of the thumb and finger allows the injection fluid to flow.

It is normal for erythrocytes to proceed through capillaries in single file and frequently under a certain degree of compression. It is therefore necessary that any suspension used for injection should have a particle size of less than 8 μ. It is also important that such particles should not flocculate, as otherwise both the cannula and the capillaries would become blocked. A material which is suitable for an injection of this type is *Monastral Fast Blue, BVS paste* produced by the Imperial Chemical Industries. The pigment paste should be diluted with water in the ratio of three parts water to one part paste. Indian ink was also found to be suitable.

In the freshly enucleated eye it is impossible to insert the cannula into the central retinal artery because the optic nerve is so soft that it moves away from the cannula. A certain amount of fixation is therefore necessary before attempting the injection. The pressure in the apparatus must clearly exceed the intra-ocular pressure and in practice a considerable excess of pressure is an advantage. The most desirable pressure is that which will give the fastest injection with the least chance of bursting the capillaries. In this connection the pressure, the bore of the cannula and the viscosity of the injection fluid are all related. For the sake of convenience the relevant figures follow in table form.

Glass tubing for cannula, ext. diam.	3	mm.
Glass tubing for cannula, bore	1	mm.
Cannula point, ext. diam.	270	microns.
Cannula point, bore	90	microns.
Injection pressure	300	mm. mercury.
Injection time	5–15	seconds.
Room temperature	65°	F.

Method

1. Fix the fresh eye in 5 per cent. formol for 30 minutes to two hours.
2. Wash in tap water 10-30 minutes.
3. Arrange the eye in a plasticine ring optic nerve uppermost, on the stage of a binocular microscope. Eyepiece x6, objective 49 mm.

4. Cut a thin slice from the end of the optic nerve so that a new, smooth surface is exposed.
5. Insert the cannula into the artery or vein and inject.
6. Place the globe in 10 per cent. formol for 24-48 hours.

Results

Although the injection is not successful in all cases the results generally are satisfactory. After the second fixation is complete the globe is bisected coronally about the region of the ora serrata

FIG 1.

and the vitreous is gently swabbed from the posterior portion. This portion is then mounted in a special holder and examined with the slit-lamp. As an example of the appearances which may be obtained in this way, Fig. 1 illustrates an injected rete mirabile

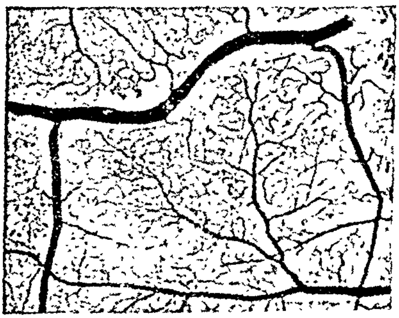


FIG. 2.

Portion of mounted retina of human eye injected after enucleation showing normal vascular system.

lying in front of the optic disc in a case of venous obstruction. The retina is subsequently peeled away from the choroidal bed and mounted on a slide in glycerine. The appearance of a portion of injected retina mounted in the manner described is illustrated in Fig. 2.

This method of examining the retinal vascular system would appear to open new possibilities in the investigation of various fundal states including the relationship between the colour of the optic disc and its capillary content, the state of the capillary bed especially at the edge of the disc in glaucoma, and its relationship to visual field defects, new-vessel formation in the retina and vitreous, the extent of the capillary free zone at the macula in various conditions, etc.

It also affords an opportunity of investigating the degree of collateral circulation existing in the optic nerve head and choroid.

Summary

1. A method is described of injecting the retinal vascular system in the freshly enucleated eye.
2. Indication is given of the possible usefulness of this new *technique*.

SEVERE LESION OF THE VISUAL PATH IN PREGNANCY*

BY

G. PERÉMY

BUDAPEST

RECENTLY I had the opportunity to review the condition of a patient whom I saw for the first time nearly 20 years ago. The case seems to be a very rare one. The case described by Lawford Knaggs more than half a century ago is closely similar to the one I am going to relate, but in the literature of the last years, as far as I had access to it, I could not trace another of that kind.

Case history.—The patient was sent in 1930 by the ophthalmologist to the First Medical Clinic of the University of Budapest for consultation on account of the rapid deterioration of the vision of her left eye. She was at that time 40 years of age and in the fourth month of her sixth pregnancy. She had already gone through three pregnancies when she accidentally became aware of the complete loss of the vision of her right eye. This happened six years earlier. In her earlier history there was nothing which could have been brought into relationship with her condition at that time, except for an apparently insignificant, slight headache which she had sometimes since her 'teens. The medical examination revealed a normal physical condition, including blood-pressure, urine and blood picture. The Wassermann test was negative. The ophthalmological data were as follows: The right pupil reacted to light only consensually, the left one only directly. Amaurosis and primary optic atrophy were found in the right eye. With the left eye she could count fingers at seven feet. The margin of the left optic disc was sharp,

* Received for publication, August 28, 1948.

and it was somewhat reddish, no papilloedema was to be observed. There was a complete central scotoma for all colours, the visual field was contracted in a high degree for red, less for white. The patient had a marked squint as a result of the amaurosis. Examination of the nervous system revealed no abnormalities. The senses of smell and taste were also normal. The pressure and the composition of the cerebrospinal fluid were normal. X-ray plates of the skull showed no signs of increased intracranial pressure. The size and the shape of the sella turcica were normal. The sinuses were clear.

The optic atrophy on the one side and the retrobulbar neuritis on the other were judged to be caused by the pregnancies. The interruption of the pregnancy of the time seemed inevitable, yet the patient left the clinic and induction was not performed until one month later, after further deterioration of her vision. I asked her to come to the clinic for re-examination. She did so two and a half years later. She said she had experienced an improvement of her vision for some months after the interruption of her pregnancy, and since then it was unchanged. She had still her menstrual flow regularly. She had no complaints. A complete loss of the temporal half of the left visual field was found. The perception of red and green in the centre of the nasal half was retained. On being asked, she related that for some time she was forced to turn her head excessively to the left when crossing a street, or else she was unaware of vehicles coming from that side. An X-ray plate of the sella showed it to be unaltered. She had put on some weight, but there were no signs of abnormalities of nervous or hypophyseal origin. The urine and the blood-pressure were normal. The findings of the ophthalmologist were as follows: The condition of the right eye was the same as at the examination two and a half years earlier. The vision of the left eye was 5/10. The left optic disc was pale. There was a temporal hemianopia. The nasal colour-fields were normal.

On re-examining the patient some weeks ago, I found that her ophthalmological condition remained unchanged. In particular the nasal colour-fields were intact. Neither could I find any other change in the condition of the patient.

There could be no doubt that this severe lesion of the visual path had been brought about by pregnancies. It could have been caused by toxic damage to the optic fibres, or by pregnancy-enlargement of the adenohypophysis, though both possibilities were equally hypothetical. The later ophthalmological findings revealed a damage to the optic chiasma or to the right optic tract too (the right eye already being amaurotic). On the basis of this condition I suggested that there might have been some benign cystic growth of the hypophysis which exerted a pressure on the chiasma mediated through the pregnancy-enlargement of the adenohypophysis. But the course of the disease and the present condition of the patient make such a hypothesis extremely unlikely. Certainly signs of increased intracranial pressure were never observed, and no change in the size and shape of the sella occurred. Neither did any other nervous or endocrine disorder develop. In a case of such a strong and repeatedly exerted pressure on the visual path which resulted in the atrophy of one optic nerve and one optic tract, other signs too should be expected, *e.g.*, a disturbance of smell, and the cardinal signs of hypophyseal-diencephalic hypofunction.* Yet no sign of that kind appeared in more than 20 years. Thus we are led to assume repeated toxic damage to the optic fibres resulting from pregnancy, which first brought about a complete atrophy of one optic nerve, and later

affected the remaining fibres of one optic tract too. Toxic damage to the optic fibres including that which is associated with pregnancy is exerted in most cases on the retrobulbar part of the axial fibres of the optic nerve, and thus arises what is known as retrobulbar neuritis. The damage to the optic fibres originating in the left retina of the patient was initiated in this way. This may support the assumption of a toxic origin, though the impairment of central vision may also be an early sign of pressure. The peculiar feature of the case presented here is that the toxic damage should extend so far along the visual path. The multiplicity of pregnancies may account for this. In such cases the task of differentiating a toxic state from that caused by a tumour in or near the sella may arise. As I tried to show, the hemianopic defect of the visual field does not prove beyond doubt that it is caused by the pressure of a neoplasm; it may be the result of the same toxic damage to the optic tract as that which affected the optic nerve. Cases may occur in which the alternative—pressure or toxic damage—cannot be decided for a while. Decision may sometimes be possible only in the later course of the disease. Fortunately in cases of pregnancy such uncertainty does not imply any therapeutical dilemma, since termination of the pregnancy is warranted in the case of an alleged tumour especially if the impairment of vision seems severe; and it is known that the growth of a hypophyseal adenoma may be stimulated by simultaneous pregnancy.

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AN UNUSUAL CONGENITAL DEFECT*

BY

ALLAN H. BRIGGS *and* D. W. MCLEAN

LINCOLN FOLKESTONE

DAPHNE S. was brought to one of us (A.H.B.) at the age of fourteen days, as the parents had noticed an abnormality of the right eye since birth. The child was normal and healthy in all other respects, and there was no family history of known ophthalmic defect. The pregnancy and labour were apparently normal.

On examination, difficult in so small an infant, it was found that the lids and adnexa were normal. The eye was white and of

* Received for publication, November 16, 1948.

normal dimensions. The cornea was clear and bright with no precipitates, but in the upper inner quadrant a pink fleshy mass was present in the anterior chamber, touching and apparently adhering to the posterior corneal surface, and occupying the whole depth of the anterior chamber in this area.

The mass was rounded and apparently solid in nature, and appeared to spring from the region of the root of the iris. It was

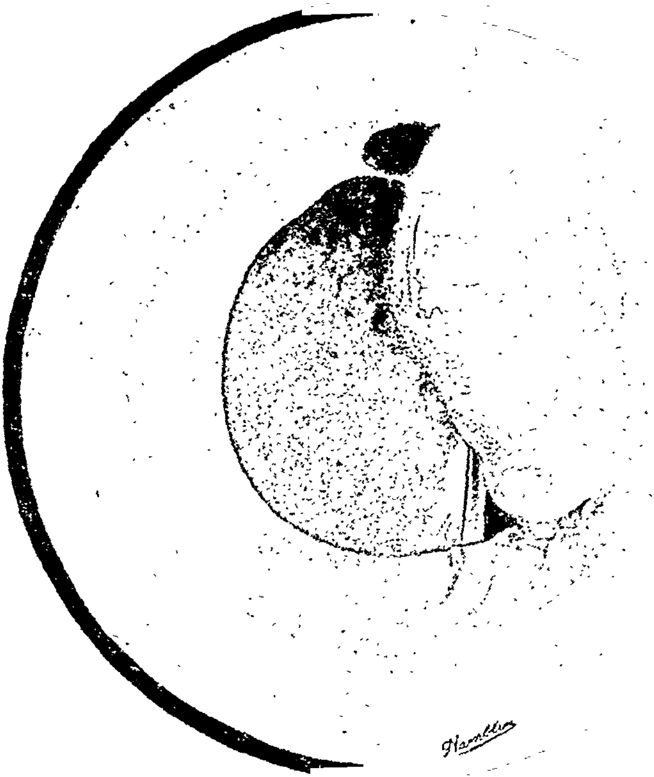

FIG. 1.

approximately 3 mm. in diameter. The anterior chamber was clear and of normal depth. The iris was normal except that there was a coloboma in the area occupied by the tumour, its margins attached to the tumour by multiple fine vascular strands. The lens was mainly clear, but with a slight posterior opacity, and there was evidence of vascular strands still present in the anterior part of the vitreous. Very little view could be obtained of the fundus,

even when the pupil was dilated with atropine, but no gross abnormality was discovered.

The child was kept under observation, and in two months it was found that the tumour was not quite so solid in appearance, and vessels could be made out on its surface. It was possible to do an approximate refraction, which showed a high degree of irregular astigmatism.

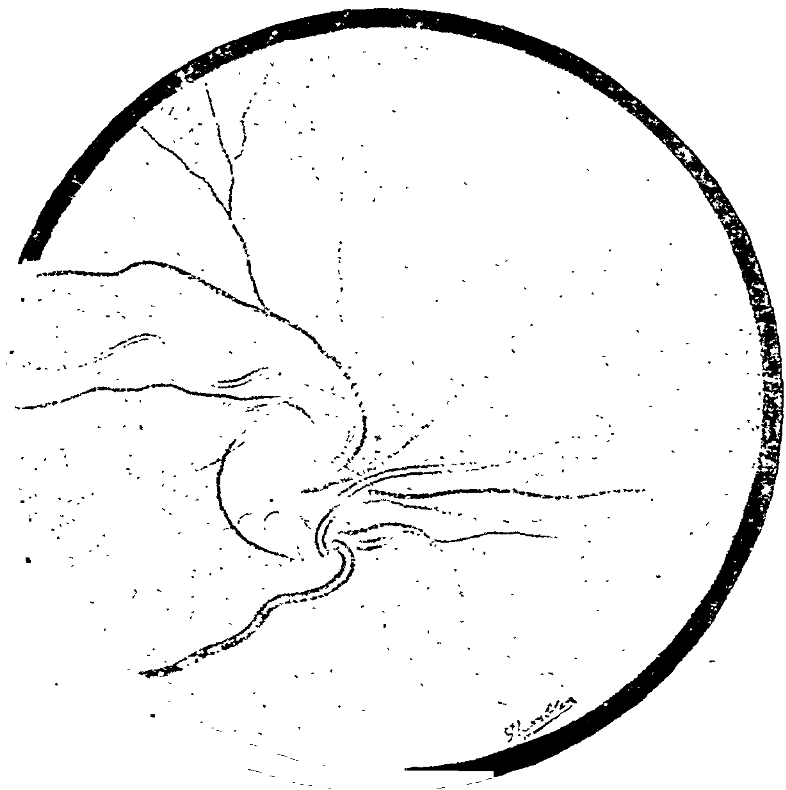

FIG. 2.

At the age of four months the condition had undergone no evident change, and further examinations at nine months and sixteen months revealed very little alteration in size or appearance.

Daphne then removed with her parents and was seen (by D.W.M.) in April, 1948, at the age of nearly six years. The occasion was the development of a right convergent squint three months earlier, following a mastoiditis which resolved without

operation. Under atropine the refraction of the right eye showed a large and irregular myopic astigmatism, and even with correction there was little useful vision. The left eye had three dioptres of hypermetropia, its vision was full and its fundus healthy.

The right eye showed a large iris coloboma on the nasal side which was completely filled by a rounded pink mass with fine vessels running over its surface. This mass extended almost half way across the dilated pupil, and protruded into the anterior chamber so as almost to touch the cornea. Over the base of the tumour the cornea showed two islands of greyish opacity resembling arcus senilis. The eye was white, and the tension was not raised. Ophthalmoscopy revealed thin strands of persistent pupillary membrane, and at the lower pole of the tumour the fibres of the zonular ligament were exposed. There was an anomalous distribution of vessels at the optic disc.

The patient's mother was able to give a detailed history of the condition, but she said that, a year earlier, a doctor had told her that the vision of the right eye was normal. Though this seemed improbable, a slight doubt was raised whether, after all, the condition were as static as it appeared, and in view of this the opinion of Miss Ida Mann was obtained. She commented (June, 1948):—

"The condition is a most unusual one and I have never seen anything quite like it. It has, however, every appearance of a congenital abnormality in that there is a coloboma of the iris, a *situs inversus* of the disc, a very high myopic astigmatism, a small tag of persistent pupillary membrane, and complete absence of inflammatory reaction or raised tension.

" . . . I am strongly of opinion that nothing should be done. I would suggest, however, that an accurate painting be made by an ophthalmic artist, which could be used for comparison six months and a year hence. If there is no change in that time I think it is perfectly safe to leave the eye alone."

Daphne was last seen (D.W.M.) in October, 1948. She had recently recovered from mumps, was in very good health, and though her strabismus was pronounced there was no discoverable alteration in the picture of her right eye.

The writers wish to express their appreciation of Miss Mann's courtesy in permitting them to quote excerpts from her letter.

A CASE OF OCULAR MYIASIS

BY

E. E. CASS

GIBRALTAR

OCULAR myiasis is rarely seen in Western Europe. It usually occurs in hot countries, where there are many flies, and the living and sanitary conditions are bad, and the people dirty and ill-nourished.

The most common fly which causes myiasis belongs to the muscoid group, amongst which the common house fly is the most usual cause of the trouble; all of this group lay eggs, usually choosing filthy situations, such as manure heaps, decomposing flesh, festering wounds, and sometimes the lids of people who are in a debilitated filthy state, with discharging eyes. If these flies do lay their eggs in the conjunctival sac, the majority lay them on the surface of the conjunctiva, but some are more dangerous, as their maggots burrow below the conjunctiva and penetrate the globe.

The oestridae possess ovipositors, and can lay their eggs beneath the conjunctiva itself, and one of them, the hypoderma bovis, can penetrate the globe. Luckily such cases of intra-ocular myiasis are very rare.

The sarcophagidae and anthomydae can also infect the conjunctiva of man.

The severity of the condition depends on the type of insect which has laid its egg in the eye, the condition of the patient, and, naturally, the longer the patient is left without treatment, the more severe is the reaction in the eye.

In the milder cases there is usually the history of a fly having entered the eye and being removed, but the discomfort does not diminish; there is increasing pain, lacrimation, and swelling of the lids and conjunctiva, and on examination the maggots are seen crawling in the eye. With removal of all the maggots the condition subsides. In the filthy ill-nourished patients who do not receive treatment, with numerous maggots, the larvae may hatch out and the whole eye be destroyed by the flies, and the orbit itself invaded, with consequent meningitis and death.

In cases of intra-ocular myiasis, intense pain and other symptoms of iritis are present. The parasite can be removed if it is in the anterior chamber, with some conservation of vision, but if it is in the retina, enucleation has to be performed. 32 such cases have been described, of which 21 occurred in the anterior chamber. In

the past 18 months 3 cases have been described in the Archivos de la Sociedad Oftalmologica Hispano-Americana; in two, larval conjunctivitis occurred, and in one of these, the patient had pre-existing trachoma. Removal of the parasites resulted in relief of the symptoms. The third case was that of an intra-ocular myiasis caused by hypoderma bovis. Removal from the angle of the A.C. of a mass, containing the parasites, resulted in relief of pain and a rapid subsidence of ocular signs and gradual return of normal vision.

The only case which has been recorded in Gibraltar is as follows: a healthy male Spaniard of 35 years was passing near a cement mixer, when he complained that some of the dust blew into his eye. A friend washed out his eye with water from a nearby tap. This occurred at 5 p.m., and the eye was immediately painful. By 10 p.m. he was suffering from intense pain, and could not sleep. His wife looked in his eye, and removed two small white bodies from it, but the pain still persisted. On the following morning he came to the Colonial Hospital, Gibraltar, sent up as a "cement burn" and immediately had his eye washed out. The nurse appeared in great agitation, saying that the man had "some white things walking in his eye." On examination he had swelling of the lids, with blepharo-spasm, pain and photophobia. The conjunctiva was oedematous and very inflamed. One small maggot, about 2 mm. long, was seen walking across the cornea, and was removed with a rod. It was pear shaped and, with the loupe, a depression was seen on the under surface of the head together with tiny suckers. The head of another maggot was seen emerging from a burrow in the conjunctiva. Cocaine 5 per cent. was inserted, and seven maggots were removed with a needle, and sent to the laboratory for identification.

The eye was irrigated with hyd. perchlor. (1:10,000), and the patient was left to wait for an hour, and then examined again. Another maggot was then removed: this had burrowed into the conjunctiva and had to be levered out.

The patient again was examined after another hour, but no further maggots were found, so the eye was irrigated, oil inserted, a flap applied, and he was allowed to return home. The next day the eye was still injected in the lower fornix, and was still slightly painful, but no more larvae were found. He was ordered irrigations and oil. Two days later there was no pain, and only slight injection below.

In this case 11 maggots in all were found. The greatest number reported in larval conjunctivitis has been 77.

The man was seeking compensation, and insisted that no fly had been in his eye, but that the maggots must have been in the cement-mixture, or the tap-water. The larvae were identified as those of Phlebotonus (sand-fly) and both cement and the tap water were examined for larvae with negative result.

It is probable that the small fly entered his eye with the dust, and was not seen by the friend who washed out the eye.

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THE LACRIMAL STRIP AND THE PRECORNEAL FILM IN CASES OF SJÖGREN'S SYNDROME

BY

M. KLEIN

LONDON.

WOLFF has recently suggested that the precorneal film has a triple structure, consisting of a deep mucoid layer, an intermediate lacrimal watery layer, and an oily layer which is very thin (probably not more than of monomolecular thickness), and which floats on the surface of the lacrimal layer.[1,2] This composite film is the product of different glands and of a mechanism to maintain it. The mucous layer derives from the goblet cells of the conjunctiva, the watery layer from the main and accessory lacrimal glands, and the oily layer from the tarsal glands. The precorneal film is maintained by the following mechanism: Whenever the eye is closed the palpebral conjunctiva comes into direct contact with the cornea, and the mucus from the goblet cells is spread over its surface. The lacrimal layer is responsible for the brightness of the corneal surface, and being completely transparent normally it cannot be seen, but after the instillation of fluorescein it shows up clearly even to the naked eye. An accumulation of this watery layer, the marginal strips, can be easily seen in the gutter formed by the lid margins touching the globe. With every descent of the lid this lacrimal strip replenishes and maintains the watery film. Apart from these anatomical and mechanical factors the relatively high protein content of the tears contributes to the evenness and stability of the lacrimal layer. The oily film can best be seen by the slit-lamp, the beam being directed on the free lid margin and the cornea illuminated by the reflected light.[3] Sometimes one can see the oily layer even with the naked eye as coloured rings, or as a fine membrane with polychromatic lustre.

It was of interest to observe the lacrimal strip and the precorneal film in several cases of keratoconjunctivitis sicca. Sjögren described how the conjunctiva and cornea lose their brightness, although as a rule they do not look dry. Though in all our observed cases Schirmer's test indicated very marked reduction in, or almost absence of lacrimal secretion, the marginal strips of tear fluid were present in all cases. The precorneal film lacked the easy-flowing flexible appearance of the normal film and was rather viscous. The oily superficial layer was also present.

Though we are dealing with keratoconjunctivitis sicca, the

* Received for publication, September 13, 1948.

marginal strips of tear fluid and the precorneal film are present, a point which so far as I am aware has not been made. Moreover the precorneal film seems to be composed of the usual three elements, but the mucoid component apparently predominates over the lacrimal film. Whether this is due to diminished lacrimal secretion alone, or the composition of the tear fluid is altered as well, needs further investigation. According to Frederick Ridley the protein content of the tears is reduced in cases of Sjögren's syndrome and in xerosis (personal communication). This may be significant, as the surface tension of the tears is influenced by the protein content, and with it the quality of the precorneal film.

My thanks are due to Mr. Eugene Wolff in whose clinic at the Royal Westminster Eye Hospital these observations were carried out, for his interest and helpful suggestions.

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THE RELATION BETWEEN PERIPHERAL RETINAL CYSTS AND DIALYSES*

BY

SIR STEWART DUKE-ELDER

LONDON

THE simultaneous occurrence of cysts at the periphery of the retina and dialyses has been remarked on several occasions, and although a close relation between the two has been suggested, I have been unable to find definite proof that a dialysis may develop from the bursting of a cyst. The following case, which by a fortunate chance illustrated this sequence, is therefore of importance.

A healthy adult male, aged 44 years, was first seen on April 16, 1946; distant vision was normal and his only complaint was of presbyopia. In the left eye, however, a typical retinal cyst, approximately 2 × 1 disc diam., occupied the extreme periphery in the usual position, down and out at about 5 o'clock. He was seen three months later, when the cyst showed no observable change. After a further three months, however, the cyst had enlarged by about one-third and, although he had no subjective symptoms, in view of the fact that he proposed to go abroad for some years, an operation was arranged, the intention being to puncture the cyst by

* Received for publication, February 14, 1949.

diathermy. He was seen again on December 2, 1946, the evening before operation, when the cyst was found to be more than double its original size. The next day, immediately before operation, a final ophthalmoscopic examination was made, and in place of the cyst a dialysis was seen occupying an area exactly corresponding to that previously occupied by the cyst, associated with a shallow detachment of the retina running a considerable way towards the disc. Diathermic coagulation was performed with a satisfactory result; six months later the retina was completely re-apposed and the vision was 6/5.

FACULTY OF OPHTHALMOLOGISTS

The following is the Honorary Secretary's summary of the business conducted at the last Council meeting on April 29:—

The following were elected Officers for 1949-50:—

President: Mr. Frank W. Law; *Vice-President:* Mr. J. J. Healy; *Honorary Secretary*: Mr. J. H. Doggart; *Honorary Treasurer:* Mr. A. B. Nutt.

It was reported that Dr. Charles Hill had written to the Ministry of Health protesting against the reduction in fee for work under the Supplementary Ophthalmic Service. It was also reported that a letter had been received from the Ministry of Health, stating that Mr. W. Penman was willing to undertake an investigation of the average time taken for a sight-test, and asking the Faculty to nominate four members to be associated with him as an informal working party to watch the investigation and study the results. Mr. Black, Mr. Healy, Mr. Gayer Morgan and Mr. Simpson have been nominated to represent both the Ophthalmic Group Committee of the British Medical Association and the Faculty.

It was learnt that the practice of referring patients from the hospital clinics to the Supplementary Ophthalmic Service did not meet with the approval of the authorities. It was agreed to write to the Ministry stating that the Faculty did not approve of this practice, but until more assistance, technically and financially, was received towards the progress of the Permanent Service there did not appear to be any alternative. It was also decided to point out that the prescriptions of the patients seen in Hospital must be made up in the Hospital; otherwise there would be no saving financially.

The draft handbook for ophthalmic medical practitioners and ophthalmic opticians, together with the comments of the Ophthalmic Group Committee, was considered. The Ophthalmic Group Committee's comments were approved, but it was felt that it should

be illegal for an optician to prescribe glasses for any case which had been referred back to the general practitioner. It was decided to recommend to the Ophthalmic Group Committee that representatives from the Committee and the Faculty should discuss this point with the Ministry, and the Chairman of the Group Committee and Mr. Law were nominated to act in this capacity.

At the suggestion of the Ministry of Health a Committee of Referees is to be set up to deal with matters arising from the regulations governing the working of the Supplementary Ophthalmic Service.

A letter was received enquiring whether a spare pair of glasses should be issued to cover the risk of breakage. It was reported that this had been referred to the Ministry of Health, who had replied that under the Supplementary Ophthalmic Service and the Hospital Eye Service a patient was not entitled to glasses if already in possession of a pair.

It was reported that a letter received from a member regarding domiciliary visits had been referred to the Ministry of Health, who had replied that if the Supplementary Service was used for bedridden patients the ophthalmic medical practitioner or ophthalmic optician could, if he wished, ask the patient for a reasonable fee for visiting him instead of the patient attending his consulting rooms. The Ministry felt, however, that all bedridden cases should be brought under the Hospital Eye Service and not the Supplementary Service.

It was agreed to call a meeting, consisting of the Officers of the Faculty and the Ophthalmic Advisors to the Regional Hospital Boards, to consider points in connection with the Permanent Service.

It was learnt that, in spite of protests from the Faculty, the Ministry of Labour and National Service had decided to reduce the fee payable to ophthalmic medical practitioners for sight tests made on and after April 1st, 1949, under the National Health Service from £1.11s.6d. to £1.5s.0d.

A request from the Joint Committee for Consultants to draw up criteria for consultants and specialists for the specific purpose of assisting those considering appeals from the decisions of the Review Committees was considered. After discussion, it was agreed to submit the following recommendations:—

1. Consultants should have ten years' approved training and experience in ophthalmology in all its branches after qualification.

2. Consultants must hold a higher degree or diploma.

3. Consultants must hold or have held a recognised appointment to a hospital.

A letter was read from the Ministry of Health giving the terms of reference and constitution of the proposed Committee on the

registration of opticians. The suggested terms of reference were "on the assumption that it would be to the public interest that provision should be made by legislation for the registration of opticians, to advise how registration could best be carried out, and what qualifications should be required as a condition of registration." The Ministry suggested that the Committee should consist of twelve members under a lay chairman to be appointed by the Minister, the members consisting of 3 ophthalmologists (1 from Scotland), 1 physician, 1 physiologist — 4 ophthalmic opticians (1 from Scotland), 1 dispensing optician — 1 physicist and 1 Member of Parliament (neither medical nor optical). The Faculty was asked to submit nominations for the first group. Though it was felt that ophthalmology was not adequately represented, it was agreed to submit nominations jointly with the Ophthalmic Group Committee of the B.M.A.

The recommendations made by the Joint Advisory Board of the Optical Profession to the Examining Bodies on the training and examination of future entrants to the optical profession were considered. It was decided :—

(*a*) That the General Anatomy and Physiology section was too detailed.

(*b*) To ask for further information regarding the examination in the use of drugs.

(*c*) That the section dealing with Abnormal Ocular Conditions in the syllabus and in the examination should be deleted. It was agreed that opticians who worked in hospitals would have an opportunity for practical experience in recognising diseases, but that this should not form part of the qualifying examination.

The question of lecturing to opticians again arose. Although the Council felt that there was no objection to members giving an occasional lecture on an optical or medico-political subject, it was agreed that a final decision could not be made until the report had been received from the Commission on the registration of opticians.

A memorandum on the practice of orthoptics has been prepared and will shortly be published in the British Medical Journal.

Regarding the proposed changes in the system of the training of nurses, it was decided to ask Mr. Law to approach the ophthalmic matrons to enquire what action had been taken, and to raise the matter with the Royal College of Nursing.

It was realised that the Regional representation on the Council left something to be desired, and letters pointing this out had been received by the Honorary Secretary. It was finally decided to alter the regions to correspond with those defined under the National Health Service. The Council will be reconstituted as follows:—

(*a*) One Member elected from each Region under the National Health Service (14).

(*b*) One Member from Scotland.

(*c*) One Member from Northern Ireland.

(*d*) One National representative from the Full and Part-time Associates.

(*e*) Eight National Member representatives.

Such an arrangement would leave its total number unchanged.

BOOK NOTICES

The Management of Binocular Imbalance. By E. KRIMSKY (New York). 464 pages, 200 figs. Henry Kimpton (London), 1948. Price 63/-.

A number of books on the ocular muscles and the problems of their imbalance have appeared in recent years, but this volume has the very considerable merits of being at once interesting and stimulating. It takes as its text the corneal reflex, and shows how this can be exploited by means of the simple equipment of a flash-light and prism to form the basis of an extremely complete objective and subjective analysis of the binocular function and state of motility. The corneal light reflex has, of course, been employed for many years by such investigators as Hirschberg, v. Graefe, Priestley Smith, Tscherning, Landolt and innumerable others in the investigation of squint, but no one has yet attempted so thorough an exploitation of its potentialities as to include not only an examination of monocular and binocular fixation, the angle of latent and manifest deviation in squint, but also, among other things, the measurement of the depth and area of suppression in a deviating eye, the elicitation and location of abnormal correspondences and false projection, the proof of the existence of diplopia and the analysis of head-tilt. The theory of the method is well-known: the corneal "reflex" is an erect virtual image formed behind the cornea which in the normally fixing eye occupies a "neutral" position centrally (apart from the angle gamma) in the pupillary area; on the displacement of the eye out of the normal position of fixation, the reflex is also displaced, and can be restored to the neutral position by placing the appropriate prism in the required position in front of the cornea. Latent deviation can similarly be estimated by dissociating the two eyes with a prism

acting at right angles to the direction of ocular deviation and again restoring the corneal reflex to a symmetrical position. By exploiting to the full these elementary principles with the aid of the simplest apparatus the author has built up a most comprehensive and thought-provoking treatment of his subject.

Everyone will not agree with him on all his conclusions, such as the valuelessness—or sometimes the dangers—of total occlusion. He himself has strictures to make upon such matters as the value of the existing tests in Air-Force examinations and screening tests for industrial workers, all of which are of interest. On the whole the book—which is excellently produced—is of considerable value and worth study.

Dermatologie für Augenärzte. (Dermatology for the Ophthalmologist). W. SCHÖNFELD. Pp. 109., 47 figs, 45 colour plates. G. Thieme Verlag (Stuttgart), 1947.

This is a very useful contribution to ophthalmic literature, for the diseases of the skin which have an ophthalmological bearing and present problems, frequently of considerable difficulty to the ophthalmologist, are many. The first part of the book gives a concise and clear discussion on the three main diatheses which influence the incidence of such diseases—the seborrhoeic, the exudative (scrofulous) and the allergic; there follows a description of the techniques of skin tests and a review of general information regarding the various types of medicaments used therapeutically (lotions, ointments, pastes, etc.). The remainder of the book describes in a systematic way the various skin diseases which may affect the lids, including neoplastic conditions and affections of the brows, lashes and associated glands. The writing is clear, the clinical photographs good, and the atlas of coloured illustrations at the end of the book excellent.

Einführung in die Augenheilkunde. (Introduction to Ophthalmology). P. A. JAENSCH. Pp. 228, 185 figs. G. Thieme Verlag (Stuttgart), 1947.

This elementaty text-book of ophthalmology suitable for the general student has much to recommend it. It is small and compact, clearly written, well illustrated and confines itself to the essentials of the subject. The usual systematic arrangement is adopted—a description of the anatomy, physiology (including optics) and embryology of the visual apparatus is followed by a systematic discussion of the pathological conditions affecting the eye and its adnexa, particular attention being paid to the aspects of ophthalmology which impinge on general medicine. For its intended audience the book is good.

OBITUARY

FRANK GRIFFITH THOMAS

We regret to have to record the death of Frank Griffith Thomas, aged 76 years, on March 22, at Bournemouth, where he had recently been living in retirement.

His passing removes another link with the pioneers of provincial ophthalmology, for his father, Dr. Jabez Thomas of Swansea was one of those medical practitioners, who during the latter part of the 19th century, by reason of a clinical flair allied to wide knowledge and force of character, gradually assumed the rôle of consultant in provincial towns. Jabez Thomas devoted much of his time to the study and treatment of eye diseases, and eventually was responsible for the opening of an eye department at the Swansea General Hospital.

Frank Thomas received his scientific and early medical training at Cambridge where he graduated B.A. (National Science Tripos) in 1893. He finished his training at Guy's Hospital where after graduating M.B. B.S. in 1897 he became House Physician and Clinical Assistant. Concentrating on ophthalmology, he acted as a Clinical Assistant at Moorfields, and later became Registrar at the Royal Eye Hospital before returning to Swansea in 1900, where he succeeded his father as Honorary Ophthalmic Surgeon to the Swansea General and Eye Hospital. He shortly afterwards married Dr. Florence Margaret, daughter of the late Dr. Price of Carmarthen, and herself an ophthalmologist, who assisted her husband in his work. His hospital and private practice developed rapidly, and it was not long before he was recognized as a leading ophthalmologist in Wales. He was a neat and careful operator, who adhered to well-tried and orthodox technique, which his excellent results more than justified. Moreover, he was not only a sound ophthalmologist, but also an experienced Physician, whose belief in his own abilities gave him an assured manner with both patient and doctor. In abstruse or difficult cases, however, he was always ready to call a colleague into consultation. In his earlier days he was frequently seen at clinical meetings as a member of the Ophthalmological Society of the United Kingdom, the South West Ophthalmological Society, and a founder member of the Oxford Congress. He acted for many years on the General Committee of this Journal.

His spare, well-groomed figure and lean features with clipped moustache suggested a military background; never effusive, he had the quiet assured manner of one who, having pondered his problems, came to definite conclusions, and was rarely prevailed upon to alter

them. He always seemed to have his emotions under control, and only a twinkle revealed his sense of humour or a tightening of his jaw muscles his displeasure; he rarely displayed anger in his speech. He enjoyed the company of his friends, whom he chose with care, and he was fond of all sports, but golf, at which he had a single figure handicap, was his favourite form of recreation.

To a large circle of friends, colleagues, and to innumerable patients, his was a personality which will be remembered and mourned. To his widow and family we tender our deepest sympathy.

J.J.H.

CORRESPONDENCE

RECESSION OF THE INFERIOR OBLIQUE

To the Editorial Committee of

THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—I have read with interest the article written by Mr. Ivor Lloyd on the subject of recession of the inferior oblique muscle, but I doubt whether the writer's view concerning the cause of overaction of the inferior oblique is as convincing as that of Chavasse. According to Chavasse* the "elevation in adduction" in a case of convergent strabismus free from obvious paresis of the ipsolateral superior oblique, or contralateral superior rectus, is due to the fact that, when an eye is adducted, the inferior oblique's elevating action is intensified because it is a stronger muscle than its direct antagonist —the superior oblique. Chavasse's explanation is more likely than Mr. Lloyd's. The latter argues that an effort of abduction which involves overaction of the inferior oblique is made in order to counteract excessive convergence.

I agree with the writer concerning the need for correcting both the horizontal and the vertical components in squint, but it is open to question whether there is any advantage in performing a recession of the inferior oblique rather than the simpler procedure of myotomy or myectomy.

It would have been more convincing if the case-results had contained not merely the statement that the overaction of the

*CHAVASSE, F. BERNARD (1939).—*Worth's Squint*, 7th edition, London.

inferior oblique had been corrected, but rather the actual measurements of vertical deviation, both before and after operation—including those made with the eyes in laevo- and dextro-version.

Yours faithfully,

T. KEITH LYLE.

May 12, 1949.

NOTES

Deaths

As we go to Press we regret to learn of the death of Dr. D. M. Mackay, formerly Ophthalmic Surgeon at Hull Royal Infirmary. Also of Dr. George Mackay, formerly Lecturer on Ophthalmology in Edinburgh University. Obituary notices will appear in our next issue.

* * * *

Ophthalmological Society of Cordoba

THE next General Meeting of the Ophthalmological Society of Córdoba takes place on November 25, next, for the purpose of re-appointing the office-bearers. Those remaining in office are as follows:—

President, Dr. Roberto Obregón Oliva; *Secretary*, Dr. Alberto Urrets Zavalia (hijo); *Treasurer*, Dr. Roque A. Maffrand,

Any correspondence should be addressed to The Secretary, Calle 27 de Abril 255, Córdoba (R. Argentine).

* * * *

AN exhibition for the blind and the partially blind has been arranged in the Science Museum, South Kensington, from June 11 to 21. This exhibition is not open to the general public, but the organisers will be pleased to welcome those who are specially interested in the welfare of the blind.

Papers submitted for publication should be sent to:—
The Secretary of the Editorial Committee,
British Journal of Ophthalmology,
Institute of Ophthalmology, Judd Street, London, W.C.1

Papers should be accompanied by a statement that they have not already been published elsewhere, and that they will not subsequently be offered to another publisher without consent of the B.J.O. Editorial Board.

All papers must be typewritten in double spacing on one side of the paper only, with a blank margin of 1½ inch. The Author's name and address should be plainly indicated. Illustrations should be detachable from the typescript, and numbered in sequence; and the upper edge of each should be marked "TOP" for the printer's guidance. Each illustration should be marked on the back with the author's name. References to the literature should be listed with the authors' names alphabetically arranged, and set out in the Harvard system, *e.g.*, LANGLEY, J. N. (1919). *J. Physiol.*, 53, 120. Information concerning reprinted copies will be despatched with galley-proofs to the authors of articles accepted for publication.

THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

JULY, 1949

COMMUNICATIONS

TOXOPLASMOSIS, A SUMMARY OF THE DISEASE WITH REPORT OF A CASE*

BY

HAROLD RIDLEY

LONDON

PRE-NATAL infection of the eyes of human infants by toxoplasma has been reported with increasing frequency in the past ten years, mainly in America, and more recently in Holland and other European countries. There are now more than 50 recorded cases. The disease was introduced to British literature by Vail in 1942, but so far only two cases have been reported in England, one by Jacoby and Sagorin in December, 1942, and one since then by Wilson and Forest Smith. A third case may, therefore, be of interest, and will perhaps draw further attention to a disease undoubtedly present in this country and often overlooked. In retrospect it is certain that cases of this disease have been seen

* Received for publication, May 3, 1949.

in the past and pronounced correctly but inaccurately intra-uterine uveitis or pseudoglioma, or incorrectly congenital developmental abnormalities including macular coloboma.

Janku in 1923 reported choroido-retinitis in the eye of an infant in which he demonstrated a protozöon which he described as a sporozöon. It is now agreed that the organism was in fact toxoplasma, and this case is accepted as the first of human toxoplasmosis recorded. Similar cases were reported by Torres (1927), Richter (1936), and Wolf and Cowan (1937). In 1939 Wolf, Cowan and Paige recognised the infecting protozöon as toxoplasma from its resemblance to that organism which was previously known to affect rodents. Since then reports of human cases have been published by numerous authors, and the disease has been carefully studied by Cowan, Wolf, Paige and others in America, and by Binkhorst in Holland. A brief summary of their researches may be of value.

The organism.—Toxoplasma was discovered in 1908 by Nicol and Manceau in the North African gondi. It is a protozö now considered by Sabin and Olitsky to be an obligate int cellular parasite. In its "free" and pathogenic form it i slender lunate or slightly curved body measuring 4-7 × microns, becoming increasingly globular with age. Stained Giemsa the cytoplasm is eosinophilic, and the nucleus hy chromatic. It is also found in multi-nuclear clumps or "cy measuring 20-30 microns, and these probably represent a gations of immature organisms. In this form it appears to no tissue-reaction so long as the enveloping cell-membr unbroken. The organism is demonstrated most readily in sections of *post mortem* material, heart, lung, mus testis, as well as in the brain and eye, but it may also be re in living patients in the cerebro-spinal fluid, and r centrifuged blood serum.

Animal infections.—Toxoplasmosis has been recog more than 40 years as a disease of rodents. It also aff It has been found in numerous wild animals, includin and zoo animals in England, and it is important to spontaneous cases have been recorded in domesti including the dog and fowl. Mice and rats are also and undoubtedly there is an extensive animal rese parasite. How the infection is transmitted to ma known. Possibly the mouse and rat, so numerous in are important carriers, though spontaneous toxoplas yet been reported in wild specimens. Ticks have b as possible insect vectors between animals, and be and man.

Human infections.—In human infections the severity of the disease and its predilection for the eye and central nervous system appear to vary inversely with the age of the patient. In adults the disease is slight, and may even be sub-clinical, though more often there is a febrile disturbance with mild broncho-pneumonia and a papillo-macular rash resembling that of typhus. Rarely a chronic encephalitis may occur. In children the disease is manifested as an encephalitis, and in infants a severe intra-uterine or early post-natal encephalo-myelitis develops, and it is this type which has up to now interested the ophthalmologist, on account of the regularity with which the eyes are involved. The eye infection is probably directly transplacental, though possibly the organism may reach the eye from the infected brain *via* the cerebro-spinal fluid along the optic nerve. It remains to be discovered whether ocular involvement follows infection other than intra-uterine, for if children infected post-natally develop an encephalitis this would not seem improbable.

General manifestations.—In severe infections the infant may die before or shortly after birth. Advanced toxoplasmosis has been found in a stillborn baby. In milder cases there may be jaundice, convulsions, spastic deformities, splenomegaly, hepato-megaly and widespread focal encephalitis leading, if the child survives, to multiple areas of cerebral calcification. These calcified areas are clearly shown by X-ray, and provide a valuable aid to diagnosis. They are found scattered throughout the cortex of all the lobes, as well as in the basal ganglia and thalami, and are of two types—curvilinear streaks, and globular bodies some 3 mm. in diameter. Internal hydrocephalus generally results, but microcephaly may occur instead. There is a varying degree of mental retardation, which in the mildest cases may be little more than delayed development of speech. Severe involvement of the eyes still further impedes progress.

Ocular manifestations.—These are practically universal, and constitute a cardinal feature of the disease.

The lesions in the two eyes are generally strikingly similar. Searching nystagmus associated with macular lesions is usual. Microphthalmos and other effects of arrested or abnormal ocular development are common, though not invariable. Gross persistence of pupillary membrane may be a feature, and less frequently posterior cortical cataract, posterior lenticonus and other developmental abnormalities may be found. Strabismus is common.

The characteristic disturbances are found in the posterior segment, and consist of focal choroiditis affecting both macular regions as well as, generally, areas elsewhere in the fundi. Frequently the periphery of one or more quadrants is involved.

The active stage, not often observed, presents the appearance of one or more brawny red swellings in the fundus, particularly at the macula, in the centre of which there is a marked tendency towards necrosis. The inflammation is strictly focal, unaffected areas of the retina and the retinal vessels remaining normal. The vitreous likewise remains clear, except in close relation to foci of inflammation. The quiescent stage is, of course, more commonly seen. In this there are sharply demarcated, punched-out white areas of choroido-retinal atrophy, sometimes as much as 6 disc-diameters across. The edges may be scalloped, as often obtains in other forms of infantile choroiditis, and there is marked pigmentary disturbance, large masses of black pigment being found at the edge of the crater and, to a lesser degree, on its floor. Sometimes bands of grey connective-tissue, often very extensive, run in the vitreous from crater to crater. In this stage, too, the unaffected areas of retina and the retinal vasculature show no abnormality, and the vitreous in general is strikingly clear. Some degree of optic atrophy is usual. This may be consecutive and associated with retinal damage, especially at the macula, or post-papillitic as a result of encephalitis.

Histopathology.—Sections show areas of acute round-celled infiltration in the choroid and retina, with a marked tendency towards necrosis. The focal nature of the lesion is shown by the sharp margin between normal and inflamed tissues. The parasite has been demonstrated within inflamed areas. Following destruction of the retina there is a proliferation of glial tissue into the vitreous. Brain sections show similar granulomatous changes, and here the necrosis is followed by calcification. In the optic nerve slight perivascular infiltration may be seen.

Laboratory tests.—The cerebro-spinal fluid is usually xanthochromic, contains excess of protein, and may show a mild pleocytosis. In a proportion of cases the parasite has been found, but since most are seen only after the acute stage has subsided, a negative result may often be expected.

Serum reactions on the patient and mother are a valuable aid to diagnosis, and are of two types. A complement-fixation test can be performed, and the titre is an indication of the activity and severity of infection. An antibody fixation test (Sabin and Ruckman, 1942) is also employed. Tissue, usually mouse brain, known to be infected with toxoplasma is mixed with the serum of the patient, and also with that of a control, and injected intracutanously into a rabbit. A nodular necrotic lesion develops about the fourth day if no antibodies are present in the serum, and fails to develop if they are present.

In some cases this test has proved negative during the first ten

weeks of the disease, and such a result probably indicates a low degree of serum reaction at this stage. A negative report, therefore, does not disprove the diagnosis. Transmission of the disease to animals by injection of infected human cerebro-spinal fluid has also been performed.

Differential diagnosis.—The disease requires differentiation mainly from other forms of intra-uterine or neonatal uveitis, and "pseudo-glioma." Among these are congenital syphilis, metastatic choroiditis associated with pulmonary infections, and choroiditis secondary to meningitis. Multiple congenital abnormalities are usually present in toxoplasma owing to arrested development of the eyes, and the central areas of choroiditis may be mistaken for bilateral colobomata of the maculae of maldevelopmental or hereditary origin. Retinoblastoma may be suggested, though the findings are not very similar. Birth injuries involving the maculae with organisation in an extensive vitreous haemorrhage may be considered. Among rare conditions Tay-Sachs' disease may occasionally be suspected, and tuberous sclerosis has certain points of similarity, including areas of cerebral calcification, though its age-group is different. The diagnosis of toxoplasma will probably be reached if its possibility is considered, and it may be supported by the evidence of skull X-rays and serum reactions, or proved by demonstration of the parasite.

Treatment.—There is clearly no prospect of improving retina already destroyed, but the child may be treated in the active stage of the disease, and the mother during or before other pregnancies. So far chemotherapy has proved disappointing. Penicillin is ineffective, but sulphonamides, though inactive *in vitro,* seem to be effective *in vivo.* One cure has been claimed by the administration of sulphonamides and emetine. It is hoped that other drugs, especially organic preparations of arsenic and antimony, which are effective against other protozöal and Leishmania infections, may prove successful, since the organism is rather highly differentiated.

COMMENTARY

It is evident that any active or quiescent choroido-retinitis which may have originated in early life, especially if it is associated with convulsions and unusual skull size, or abnormal development of the eyes, should suggest the possibility of toxoplasmosis. The characteristic lesions in the eyes are bilateral areas of focal choroiditis, frequently multiple, and almost invariably affecting both maculae. The intervening retina and

the retinal vasculature are normal. The vitreous is clear, but extensive bands of connective-tissue may run through this structure between areas of choroiditis. Associated ocular deformities, particularly microphthalmos and marked persistence of pupillary membrane, are common. In addition to the eyes and brain, other organs, especially the liver and spleen, may be infected. In suspected cases skull X-rays and serum-reactions on child and mother and siblings should be performed. Among the many problems awaiting solution are the mode of transmission, the possibility of ocular toxoplasmosis occurring in other than congenital infections, and the treatment of the disease.

CASE REPORT

A. H., a boy now aged two years and eleven months, was first admitted to St. Thomas's Hospital, London, at the age of six weeks for investigation, having been fretful and irritable and suffering from vomiting attacks for three days. The mother, who is rather deaf, reported that her health during pregnancy was good, and that labour was normal. The child's birth-weight was seven pounds, and there was no neonatal jaundice. Though a cat and a dog are now kept, there were no domestic animals except racing pigeons at the home before the patient's birth, but the house was infested with mice. In the course of examination hepatomegaly and splenomegaly were found, and the lungs were normal. A convergent squint was present, and defective vision was suspected, since the child did not appear to notice surrounding objects. The blood count was as follows:—R.B.C. 3,520,000.

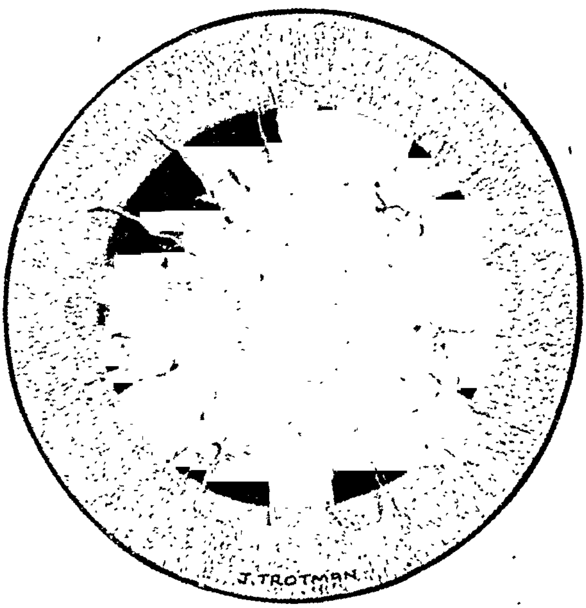

FIG. 1.

Persistent pupillary membrane in right eye.

Hb. 60 per cent. W.B.C. 20,600. Polymorphs 12 per cent. Lymphocytes 80 per cent. Mononuclears 4 per cent. Eosinophils 2 per cent. Pathological monocytes 2 per cent. Normoblasts 2 per cent. The blood-Wassermann reactions of mother and child were negative. One week later a gluteal abscess was incised, and three months later other septic blisters appeared on the buttock, and there was a sharp vaccination reaction. At the age of eighteen months there had been one convulsion, with foaming at the mouth.

The child was brought to the eye department when aged two-and-a-quarter years on account of squint and defective vision. He appeared rather backward for his age, but could see and grasp objects of moderate size, and would run by himself

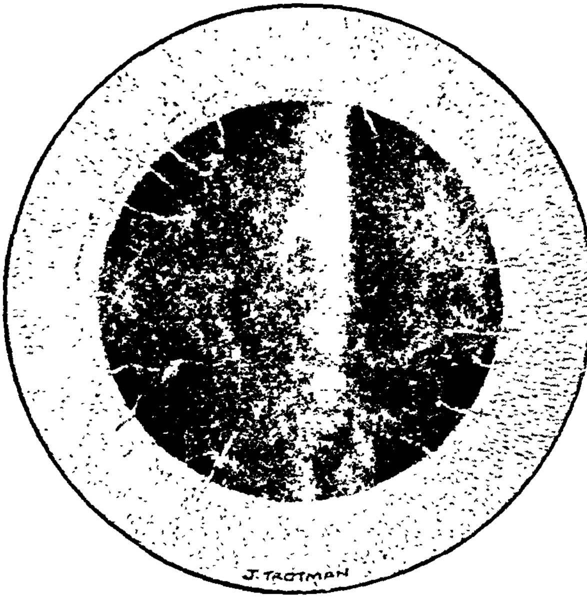

FIG. 2.

Persistent pupillary membrane in left eye.

around the room in play without knocking against furniture. On examination there was right convergent strabismus of about 25 deg., with apparent weakness of the external recti, and slight epicanthus on the left side, microphthalmos, persistent pupillary membrane, congenital lens opacities, and in the right eye what appeared to be a macular coloboma and a patch of connective tissue in the upper nasal quadrant. He was thought to be suffering from multiple congenital malformations. Unfortunately six months elapsed before he was seen again for examination under general anaesthesia. The child is hydrocephalic, the skull circumference being $19\frac{3}{4}$ inches. The fontanelles are closed. The eyes are slightly microphthalmic, the corneæ measuring 9·5 mm. in diameter. The right convergent strabismus is unchanged, and fixation is defective. In both eyes there is very marked persistence of pupillary membrane, and localised opacity in the anterior lens capsule. The pupils react to light, and there is no evidence of past inflammation in the anterior segment of the eyes. Owing to these abnormalities a clear view of the fundi is difficult to obtain. It is, however, evident that in the right macular region there is an area of choroido-retinal atrophy approximately 4 disc-diameters

in size. Large choroidal vessels are visible in the base of the crater, and there is considerable pigment disturbance, especially at the temporal edge. In the upper nasal periphery there is a patch of light grey connective-tissue lying in front of the retina similar in size to the macular lesion. So far as could be observed, there are no other abnormalities. In the left eye no definite macular lesion resembling that in the right eye could be seen but the area immediately temporal to the optic disc appeared somewhat pale, suggesting a milder degree of choroidal disturbance. Some glial tissue is visible in the upper periphery of the fundus. It was clear at this

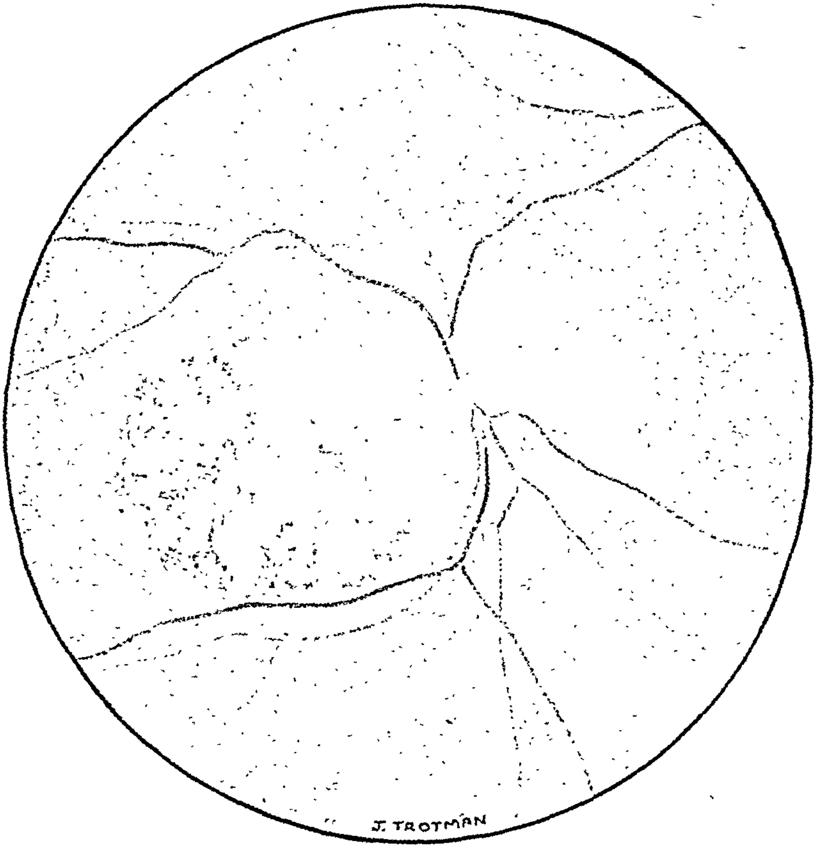

FIG. 3.

Right fundus showing macular and peripheral lesions.

stage that the case was probably one of toxoplasmosis, and that our earlier diagnosis was incorrect. X-rays of the skull, now performed, show multiple areas of calcification including one curvilinear streak in the brain. The serum-reaction to toxoplasma is strongly positive, the complement-fixation being 100 per cent. at the surprisingly high titre of 1/256. There is no fixation of normal antigens. The cerebro-spinal fluid is clear, and contains per millilitre 2 cells, 35 mg. protein with no excess of globulin, 738 mg. of chlorides and 0·069 per cent. of sugar. No parasites were found. The skull X-rays of mother, father and sister are normal, and their sera all negative to toxoplasma at a titre of 1/2.

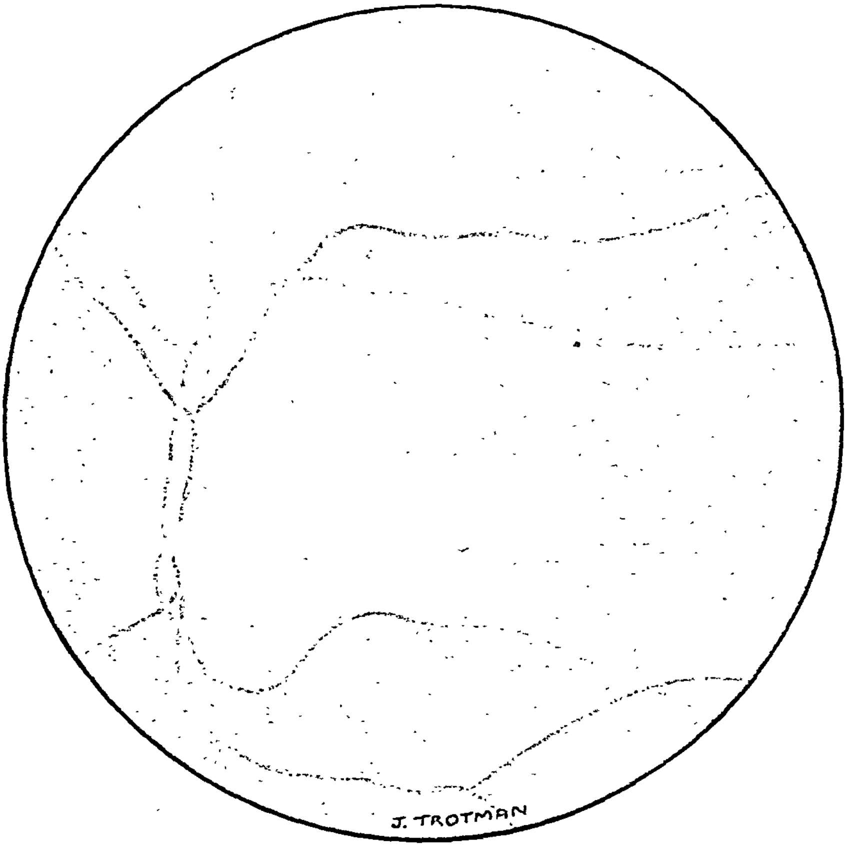

FIG. 4.

Left fundus showing similar lesions, but less conspicuous than those of right eye.

FIG. 5.

FIG. 6.

X-rays of skull showing multiple areas of calcification.

Though no toxoplasma parasites have been discovered, and it is perhaps rather late to expect a positive finding, there can be no doubt concerning the diagnosis. The mother's negative serum-reaction is difficult to explain. It is conceivable that the child acquired the infection after birth, but this would appear highly improbable in view of the extremely early age at which the sight was thought to be abnormal, and the presence of developmental abnormalities such as gross persistence of pupillary membrane. The mother is now seven months pregnant. X-rays of the foetal skull show no abnormal calcification at present, but this next child will be examined for toxoplasmosis soon after birth.

My thanks are due to Dr. J. A. Dudgeon for performing the serological tests, and to Dr. B. R. D. Wilson for information regarding the general condition of the patient.

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VASCULAR CHANGES IN DIABETES WITH PARTICULAR REFERENCE TO THE RETINAL VESSELS

Preliminary Report *

BY

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RECENT advances in pathological and clinical studies of diabetes indicate that at least some of the more important complications of this disease may have a common underlying cause, namely, a vascular degeneration. There is already an extensive literature referring to retinopathy, intercapillary glomerulosclerosis, peripheral neuritis and generalised athero-sclerosis in diabetes; their inter-relationship has been repeatedly emphasised and it is suggested that they should be regarded as different manifestations of the same underlying pathology.

Dedicated to Professor J. Meller.

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As long ago as 1921 Wagener and Wilder pointed out that retinopathy of a diabetic type was almost always complicated by vascular or renal disease, and in 1934 Wagener, Dry and Wilder studied 1,052 diabetic cases and noted the association of retinopathy with disease of the peripheral nerves, which occurred in 25 per cent. of all cases in which retinopathy was present. The possibility occurred to them that lesions like those observed in the retina may also arise in relation to the peripheral nerves, and they further suggested that similar lesions affecting the vasa vasorum of the larger arteries might contribute to the athero-sclerosis of those vessels, which occurs so frequently among diabetic patients at an earlier age than is common among persons who are not diabetic.

In 1936 Kimmelstiel and Wilson described the deposition of a hyaline material in the intercapillary connective tissues of the glomeruli of the kidney, and they were surprised to find, on reviewing the clinical data, that there was a previous history of diabetes in all their cases except one. They termed the lesion intercapillary glomerulosclerosis. Allen (1941), in an attempt to establish the significance of the renal lesion, carried their work to a further stage, and reported the examination of the kidneys from 105 consecutive patients with diabetes, 100 consecutive non-diabetic patients with hypertension, 100 consecutive non-diabetic patients without hypertension, and 34 patients with glomerulo-nephritis; the kidneys were studied with a variety of special stains, principally from the point of view of glomerular change. A characteristic focal glomerular hyalinisation of the type described by Kimmelstiel and Wilson was found in 33 per cent. of diabetic patients over the age of 40. The diabetic lesion was easily distinguishable from the glomerulosclerosis of nephro-sclerotic kidneys from non-diabetic persons and from the glomerular hyalinisation of glomerulo-nephritic kidneys, but he regarded the diabetic lesion as a focal intramural glomerulo-sclerosis rather than an intercapillary hyalinisation as had hitherto been considered. The lesion was offered as the most reliable criterion available for the histological diagnosis of diabetes mellitus in cases over the age of 40. Bell (1942) considered the nodular type of glomerular lesion as almost pathognomonic for diabetes.

Henderson *et al.* (1947) found intercapillary glomerulo-sclerosis in 19·5 per cent. of 313 diabetic patients on whom necropsies were performed. That the lesion is not completely specific is shown from the fact that it was also found in 12·3 per cent. of 81 cases of glomerulo-nephritis and in 5·2 per cent. of 134 cases in which death was due to hypertension and its compli-

cations. Severe lesions, however, were by far the most frequent in cases of diabetes. He concluded that although intercapillary glomerulosclerosis cannot be diagnosed clinically with complete certainty, it should be strongly suspected in patients who have diabetes mellitus of long standing associated with albuminuria, hypertension, renal insufficiency and diabetic retinopathy; he adds that the more advanced types of diabetic retinopathy are more or less regularly associated with this renal lesion. Kimmelstiel and Porter (1948), reviewing the accumulated experience since their first publication, stated, from a selection of statistics, that intercapillary glomerulosclerosis of the nodular type occurs approximately in 17 per cent. of all diabetics, and twice as often in women as in men. It is rare in the first two decades of life, maximum at the sixth decade, and then declines. Retinopathy occurs in 86 per cent. of cases with the advanced lesion.

In 1943, 1944 and 1945 Ballantyne and Löwenstein investigated diabetic retinopathy from the clinical and pathological point of view and came to the conclusion that it was a separate entity quite distinct from the retinopathy of hypertension. They reported upon observations of the unstained flat retina, examined in bulk, and of the retina stained in vertical and horizontal serial sections; they gave reasons for believing that the so-called punctate haemorrhages seen on ophthalmoscopical examination are in fact globular micro-aneurysms which occur, almost without exception, in the inner nuclear layer from the capillaries which link the more superficial capillary network in the nerve fibre layer with the deeper plexus at the outer boundary of the inner nuclear layer. They noted that these lesions may be a source of haemorrhage by diapedesis or rhexis, and that they may undergo a process of thrombosis and cicatrisation. Their investigations, using Sudan and Scarlet R. staining, led them to conclude that these structures, and the other venous changes of which they are a part, are due to the combination of venous engorgement with localised fatty degeneration of the vessel wall, and they postulated an unknown selective circulatory chemical toxin as the probable aetiological factor. Ballantyne (1945) stated that micro-aneurysms may occur alone and seem to be the earliest unequivocal sign of diabetes. Elwyn (1941) is inclined to regard the lesions simply as capillary dilatations rather than true aneurysms, and he interpreted them as evidence of "prestasis" in the retina; he believed that, in a person who has hyperglycaemia of prolonged duration, the persistently high sugar level influences the terminal vessel units to produce dilatation which results in stasis with a state of chronic sub-nutrition and

deficient oxygen supply, with the consequent appearance of lipoids and hyaline material.

This brief review of the literature indicates that there is now ample evidence of a proclivity to a particular type of vascular degeneration in diabetes, particularly in long-standing diabetics in the older age-groups. As might be expected, and as Stocks (1944) and Joslin (1946) have shown, diabetics are living longer since the introduction of insulin, and the complications resulting from vascular disease are becoming correspondingly more frequent. Wagener (1945) reviewed the position of retinopathy in the light of modern knowledge, and he pointed out the serious fact that the frequency of its occurrence is increasing steadily. Croom and Scott (1949) have shown, however, from a clinical examination of 60 diabetics, that vascular complications are by no means inevitable even as late as 26 years after the onset of diabetes; nevertheless, a proper understanding of the pathology of the changes in the vascular system in the diabetic is clearly one of urgency and importance.

Little work has yet been done upon the correlation of the histological changes in the retinal vessels with those in the vessels elsewhere in the body. Ballantyne and Löwenstein confined their studies to the eye, and the renal lesions have been related only to the ophthalmoscopical appearances of the retina. An investigation has therefore been started in this department to compare the histopathological changes in the diabetic retina with disease in the vascular system generally. So far the post-mortem material from 24 diabetics has been examined, but since the eyes were not available for microscopical examination in three of the cases, only 21 are reported here. It is realised that this is a small series of cases, but the number of diabetics dying in hospital is not great; post-mortems are not carried out in every case, and only in a small proportion of these can permission be obtained to examine the eyes. It has, therefore, been thought advisable to issue a preliminary report setting out our findings to date.

METHODS AND TECHNIQUE

The post-mortem material from 21 diabetics was subjected to the following investigations:—

EYES: In two cases the posterior half of the eye was removed through the orbital roof; in all other cases one or both eyes were removed *in toto*. Where the whole eye was obtained it was fixed in 10 per cent. formal saline, frozen, cut transversely through the ora serrata and the frozen vitreous removed with forceps. It was realised early in the investigation that it is unsatisfactory to remove the posterior half of the eye at post-mortem. Retraction of the retinal vessels gives rise to the formation of loops which superficially resemble aneurysms (Fig. 1 and 2): great care must be taken in interpreting the appearances of such a specimen. The eye should always be removed completely and fixed in formal saline before opening.

Retina: The posterior attachment of the retina was severed by gently twisting a small capillary tube, the size of the disc, around the nerve from the inside. The retina was then floated out of the globe in saline and mounted in a glass sphere of the same shape and size. The specimen was thus examined macroscopically and in the slit-lamp; it was subsequently photographed in the sphere to record the severity of the retinopathy and the site of the micro-aneurysms (Fig. 3). The retinae were then removed and studied in a variety of ways:—

(*a*) Flat retina stained with the per-iodic method of Hotchkiss and McManus (1948, 1946) as applied by Friedenwald (1948) (Fig. 4) and the acetic-carbol-sudan method of Jackson (1944).

(*b*) Flat retina stained by the following method, devised in this laboratory, to demonstrate the blood content of the vessels.

70 per cent. alcohol. 5 minutes.
Saturated solution of benzidene in absolute alcohol. 5 minutes.
Ozonic ether—until the blue colour is well developed.
Xylol until clear and until bubbles have ceased to evolve (usually about 15-30 minutes).
Mount flat in canada balsam.

(*c*) Horizontal and vertical serial sections of the retina were stained with haematoxylin and eosin, Hotchkiss-McManus technique, Kimmelstiel-Wilson's basement membrane stain and Wilder's silver stain.

(*d*) The unfixed retina was shaken up with saline until it disintegrated; the suspension was centrifuged and the deposit stained with the Hotchkiss-McManus method. By this means vessels could be examined separate from retinal tissue.

Iris. The pigment layer was removed by blunt dissection under saline and the specimen was laid flat and stained in bulk with the Hotchkiss-McManus method. Horizontal serial sections of the iris were also stained by this technique.

Ciliary body. In cases where diabetic retinopathy was found the ciliary body was examined by serial sections stained with the Hotchkiss-McManus method.

Choroid. The choroid was removed from the eye, bleached with chlorine gas and stained as above.

Conjunctiva. In some cases there was sufficient conjunctiva for examination and a biopsy of conjunctiva was taken from a patient with diabetic retinopathy during an operation for cataract. The membrane was laid flat and stained by the Hotchkiss-McManus method.

Viscera. The capsules of the kidney and liver, the pleura, pericardium, omentum, peritoneum and bladder wall were fixed in formal saline and examined flat, in bulk, stained by the Hotchkiss-McManus and benzidene techniques. Figs. 5, 6, 7 and 8 show the vessels stained by both methods.

Brain. The vessels of the brain were examined (*a*) by smears of the fresh brain tissue stained with the Hotchkiss-McManus technique and (*b*) by shaking the fresh brain tissue in saline until the tissue was completely disintegrated; the suspension was then poured into a flat dish and the minute vessels were picked out with forceps and examined unstained and stained with methylene blue (Fig. 9) and the Hotchkiss-McManus method.

Paraffin sections were cut of the liver, kidney, heart, brain, lung and pancreas and they were stained with haematoxylin and eosin. Further sections were stained with the Hotchkiss-McManus technique, Kimmelstiel-Wilson's basement membrane stain and Wilder's silver stain. Frozen sections of the kidney were stained with Acetic-Carbol-Sudan (Jackson).

For the staining of paraffin sections of the kidney we found Friedenwald's modification of the Hotchkiss-McManus technique unsatisfactory. The following modification was evolved in the department and excellent results were obtained:—

SOLUTIONS.

Periodic Acid Soln. A.	400 mg. periodic acid.
(Hotchkiss)	10 ml. distilled water.
	5 ml. M/5 sodium acetate solution.

Immediately before use mix 15 ml. of this solution with 35 ml. ethyl alcohol.

Reducing Rinse ... ... 1 g. potassium iodide.
(Hotchkiss) 1 g. sodium thiosulphate (pentahydrate).
20 ml. distilled water.
Add with stirring 30 ml. ethyl alcohol.
and then add 0·5 ml. 2 N HCl.
Leave for the deposit of sulphur to settle.

Fuchsin-sulphite Solution ... ... (A) 0·2 g. Basic fuchsin (as obtained from Gurr for Feulgen's reaction) dissolved in 120 ml. of hot distilled water. Cool.
(Gradwohl, Vol. 11, page 2026). (B) 2 g. sodium bisulphite in 20 cc. distilled water.

Add (A) to (B) then add to the whole 2 ml. concentrated hydrochloric acid, mix, and dilute the reagent to 200 ml. with distilled water.

Before use, leave overnight in the dark.

The solution should be a pale straw colour or colourless.

Saturated sulphurous acid ... ... To 200 ml. distilled water add
(Carleton and Leach, 10 ml. 10 per cent. anhydrous sodium
page 63). bisulphite soln.
and then 10 ml. N/1 HCl.

This solution should be made up fresh on the day of use.

Formalin fixed tissue. Paraffin sections 4 *microns* thick.

Bring sections to 70 *per cent. spirit:*

METHOD.

1. Alcoholic periodic acid. Solution A. 1 hour.
2. Rinse in 70 per cent. spirit.
3. Reducing rinse. 5 minutes.
4. Rinse in 70 per cent. spirit.
5. Fuchsin-sulphite solution. 1½ hours.
6. Saturated solution sulphurous acid 2 changes of 10 minutes each.
7. Wash in tap water 10 minutes.
8. Dehydrate quickly through spirit and alcohol. Clear in xylol and mount in canada balsam.

CONTROLS: Retinae were removed from all eyes coming to the department for routine examination and the retinae were examined flat after staining with the Hotchkiss-McManus method.

RESULTS AND DISCUSSION

To facilitate discussion our findings will be described under the questions we set out to answer.

1. *Are the vascular lesions in the retina true aneurysms (Ballantyne), simple capillary dilatations (Elwyn), nodular exudates or encysted haemorrhages?*

An aneurysm is usually defined as a localised arterial dilatation, formed by the vessel walls, within which blood circulates. Since these retinal lesions are largely confined to the venous side of the capillary network, the term is not strictly applicable to them; however, even if the name of capillary micro-aneurysm is accepted, it must still be decided whether these globular swellings on the vessels in diabetic retinopathy are vascular diverticula with walls

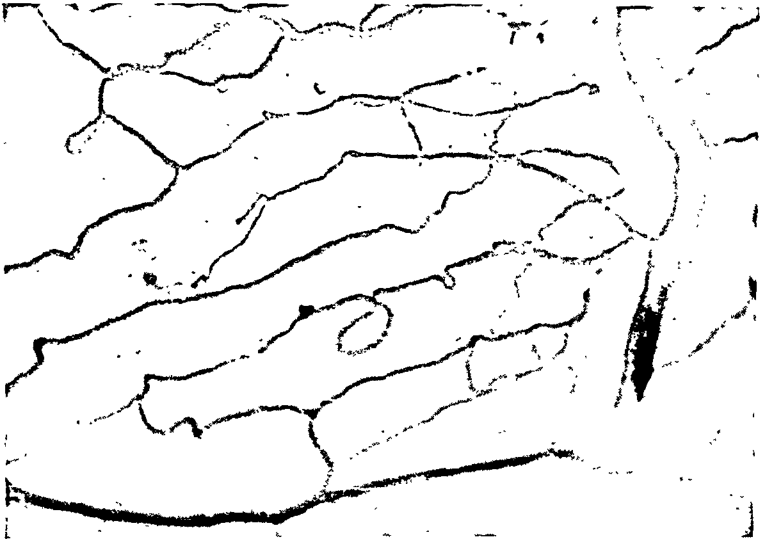

FIG. 1.

Case 8. Retina removed from the posterior half of the eye at post-mortem. The vessels have retracted to form loops which superficially resemble micro-aneurysms. Benzidene stain. × 66.

FIG. 2.

Case 8. High power view of Fig. 1. Shows looping of retinal vessels. Benzidene stain. × 950.

FIG. 3.

Case 14. Retina removed from the left eye and mounted in a glass sphere. Shows diabetic retinopathy stage III, with "dot and blot" haemorrhages scattered throughout the retina but particularly aggregated in the posterior polar region.

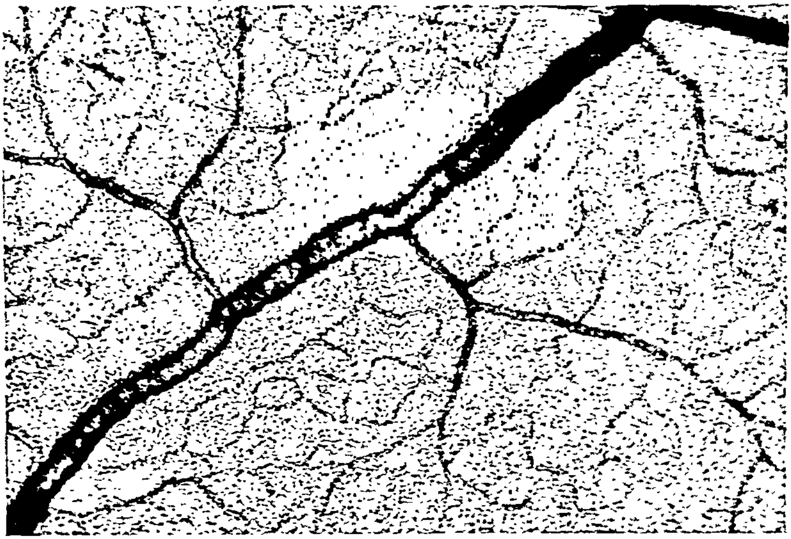

FIG. 4.

Normal retina showing the vessels stained by the Hotchkiss-McManus (Friedenwald) method. Flat preparation. × 66.

FIG. 5.

Meningeal vessels from a case with diabetic retinopathy. There is no evidence of aneurysm formation. Flat preparation. Benzidene stain. × 54.

FIG. 6.

Meninges, from a case with diabetic retinopathy, stained by the Hotchkiss-McManus technique. The vessels and corpora amylacea stain an intense red. There was no evidence of aneurysm formation. × 42

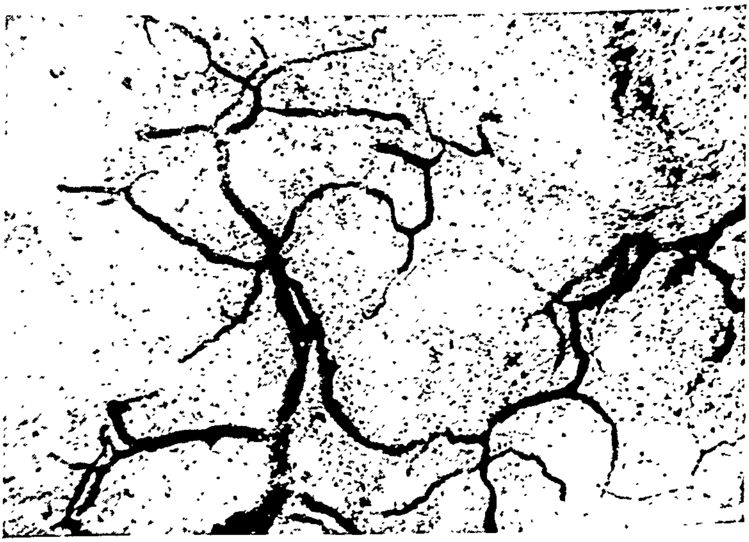

FIG. 7.

Pleural vessels from a case with diabetic retinopathy. There is no evidence of aneurysm formation. Flat preparation. Benzidene stain. × 60.

Fig. 8.

Pleural vessels from a case with diabetic retinopathy. There is no evidence of aneurysmal formation. The vessels show an intensely staining basement membrane. Hotchkiss-McManus stain. × 104.

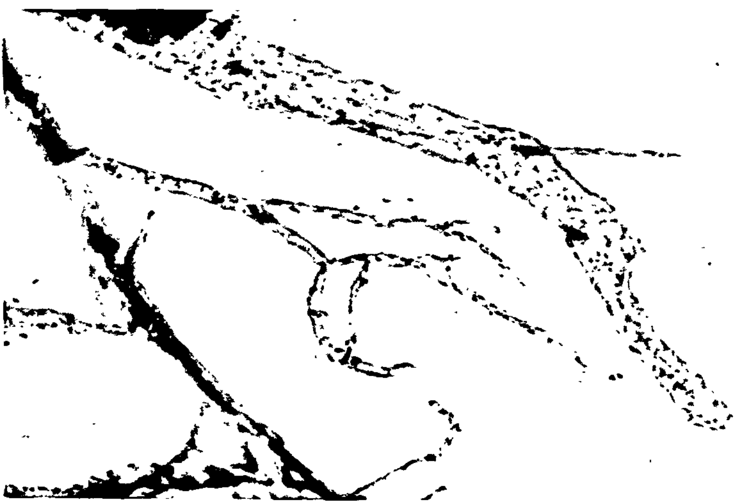

Fig. 9.

Case 15. Cerebral vessels from a case of diabetic retinopathy. There is no evidence of aneurysm formation. "Shake" preparation. Methylene blue. × 16.

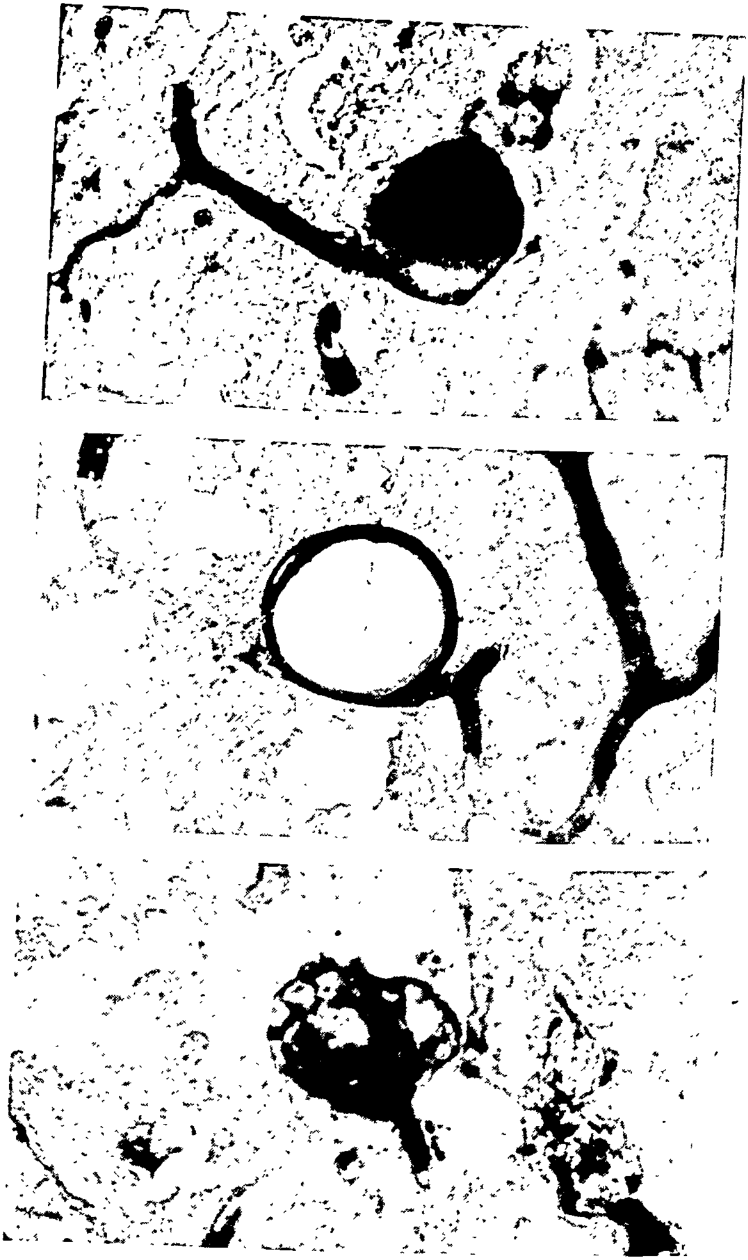

FIG. 10.

Case 14. Horizontal serial sections of the left retina. The upper section shows the inner wall of the aneurysm, the middle section passes through the centre and the lower section shows the outer wall. Hotchkiss-McManus (Friedenwald) stain. × 300.

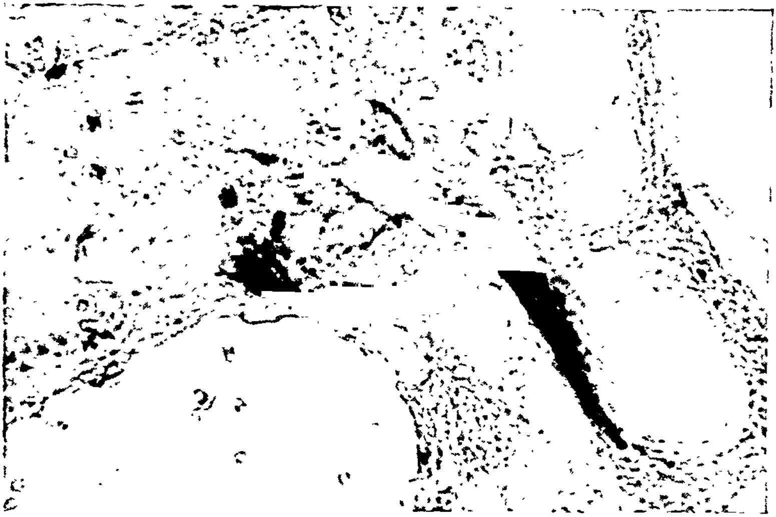

Fig. 11.

Case 21. Retinal capillary showing the vessel wall distending to form an aneurysm. Horizontal section of the retina. Hotchkiss-McManus (Friedenwald) stain. × 1066.

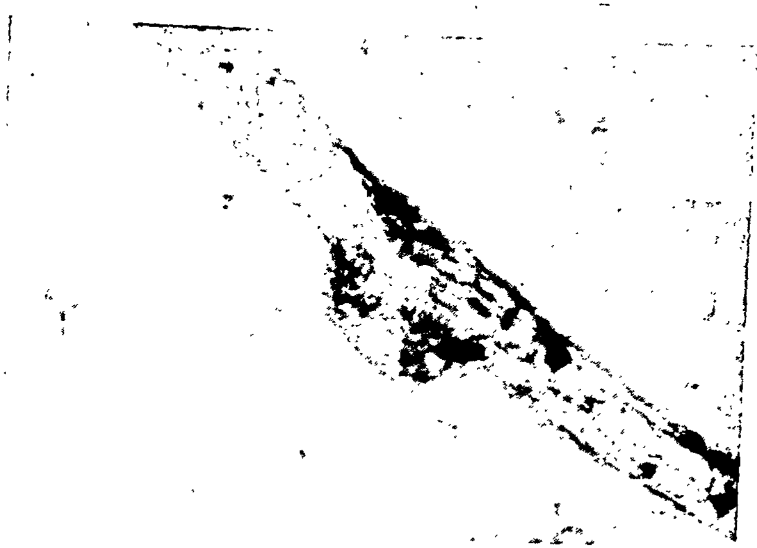

FIG. 12.

Case 21. Retinal capillary showing early micro-aneurysm formation. Horizontal section of the retina. Hotchkiss-McManus (Friedenwald) stain. × 932.

FIG. 13.

Case 15. Retinal vessels shaken free of retinal tissue. A well defined micro-aneurysm is present and the afferent and efferent vessel may be seen. Hotchkiss-McManus (Friedwald) stain. × 422. Diameter of aneurysm 77 microns.

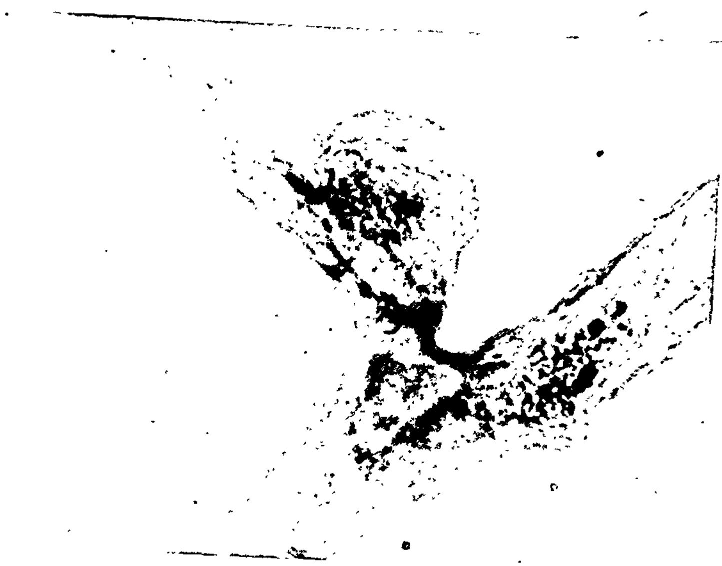

FIG. 14.

Case 15. Retinal vessel shaken free of retinal tissue. The intensely staining basement membrane can be seen extending into the wall of the aneurysm. Hotchkiss-McManus (Friedenwald) stain. × 684.

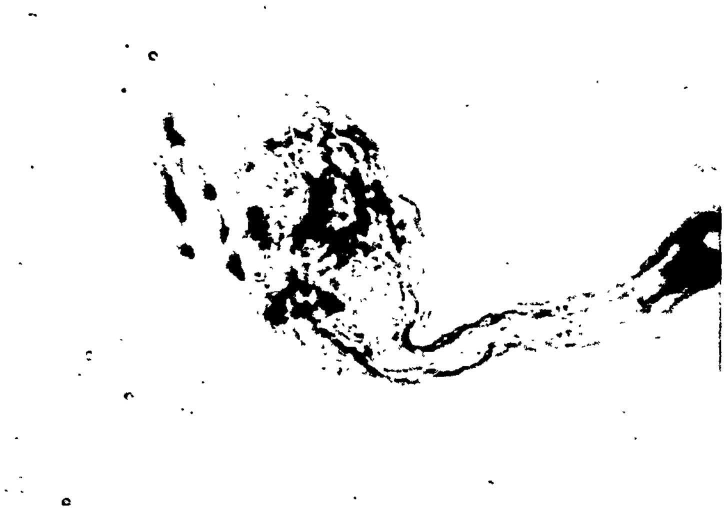

FIG. 15.

Case 15. Retinal micro-aneurysm shaken free of retinal tissue. There is degeneration and proliferation of the vessel wall: the basement membrane splits and disappears at the edge of the aneurysm. Hotchkiss-McManus (Friedenwald) stain. × 666.

FIG. 16.

Diabetic retinopathy. Flat retina stained with benzidene showing irregular haemorrhages and micro-aneurysms containing blood. × 60.

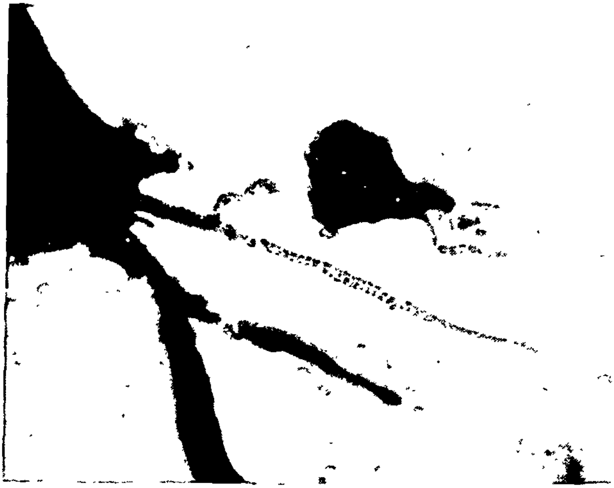

FIG. 17.

Diabetic retinopathy. High power view of Fig. 16. Shows a capillary micro-aneurysm containing blood. × 168.

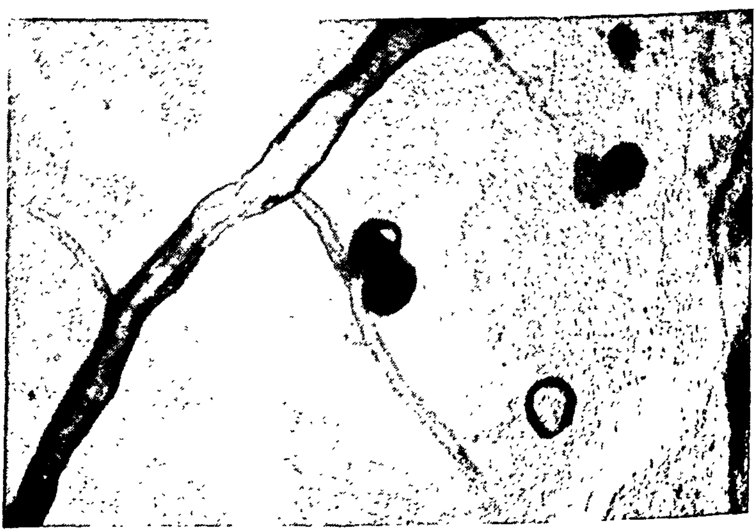

FIG. 18.

Case 14. Retinal micro-aneurysms. Left retina stained flat by Hotchkiss-McManus (Friedenwald) method. × 76.

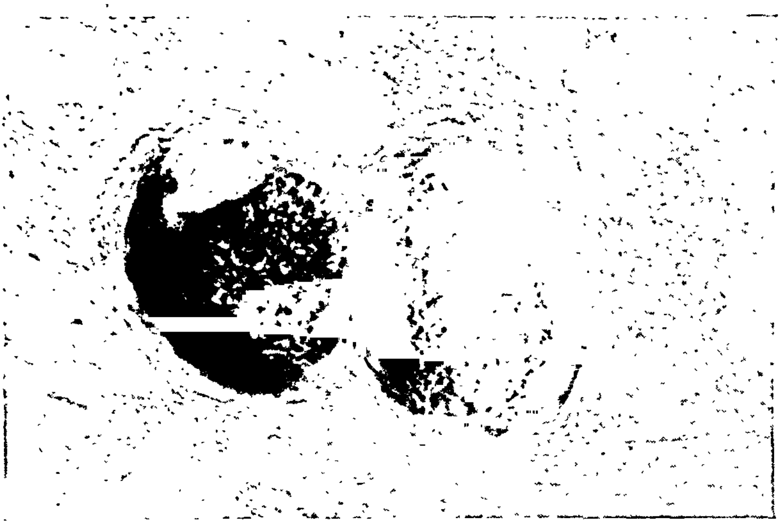

FIG. 19.

Case 14. High power view of two adjacent retinal micro-aneurysms seen also in Fig. 18. The lesions are remarkably localised and the remainder of the vessel appears normal. Hotchkiss-McManus (Friedenwald) stain. × 390.

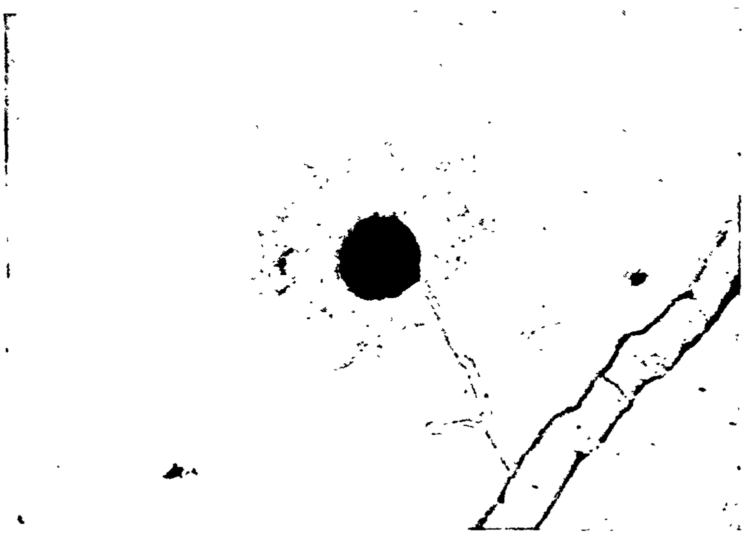

FIG. 20.

Case 14. Micro-aneurysm with surrounding haemorrhage. Left retina stained flat. Hotchkiss-McManus (Friedenwald) method. × 120.

FIG. 25.

Case 24. Nodular type of intercapillary glomerulosclerosis showing localised dilatation of the vessels. Paraffin section H. and E. × 254.

formed by the coats of the vessels, or whether they are lesions unconnected with the vessel lumen. There is already considerable evidence that they are true aneurysms, for Ballantyne has shown that many of them at least are connected to a vessel, and his examinations of the flat retina have demonstrated blood within them. More recently, Friedenwald (1948) has applied the technique of Hotchkiss and McManus to the flat retina, and he has demonstrated the lesions in a most striking way. By this method polysaccharides are oxidised to polyaldehydes by periodic acid and the preparation is then stained with fuchsin-sulphite (Schiff's reagent); the exact details of the technique are given in Friedenwald's paper. Even better differentiation can be obtained if the rods and cones are first brushed off with a fine camel-hair brush. The vessel walls stain red and a more intensely staining basement membrane may be seen beneath the vascular endothelium. Friedenwald regarded the vascular nodules in diabetes as true aneurysms because they had an afferent and efferent connection; although this is a point in favour, it is not completely convincing, and we have sought to obtain an actual section of one of these lesions at the site of its vascular origin. This was eventually obtained in a series of horizontal sections of the retina, stained with the Hotchkiss-McManus method (Fig. 10), and it leaves little doubt that these vascular nodules are in fact true aneurysms. This is further supported by Fig. 11, which shows the vessel wall distending to form the aneurysm. Aneurysmal formation at an early stage is shown in Fig. 12. Figs. 13 and 14 are vessels floated out of the retina as described earlier; Fig. 13 clearly shows the afferent and efferent vessels. and Fig. 14 shows the basement membrane continuing into the aneurysmal wall; and Fig. 15 shows not only aneurysmal formation, but also degeneration and proliferation of the vessel wall. It will be seen that the basement membrane disappears suddenly at the edge of the aneurysm. That the aneurysms contain blood is clearly shown in the flat retina stained by the benzidene method (Figs. 16 and 17); this was further demonstrated in serial sections stained with haematoxylin and eosin. One of the most striking features of these lesions is that their point of origin may be extraordinarily localised. In most cases they arise from one side of the vessel only, while the opposite side appears perfectly normal, showing no signs of distension. The two aneurysms shown in Figs. 18 and 19 apparently arise from two adjacent foci, which must have been remarkably well circumscribed by healthy tissue for such a lesion to have resulted. Fusiform aneurysms are uncommon; the majority are saccular diverticula.

From this evidence we are, therefore, able to confirm Ballantyne's original contention that these lesions are true micro-aneurysms.

2. *Where are the aneurysms situated in the retina?*

It has long been known that the fundus haemorrhages in diabetes are at first confined to the macular and peri-macular area and that they take the form of "dots and blots." In the later stages they become larger and more widespread while more irregular haemorrhages then predominate. The Hotchkiss-McManus staining technique as modified by Friendwald demonstrates better than any previous method that the well defined "haemorrhages" are all micro-aneurysms and that the irregular haemorrhages are extravasations of blood usually related to an aneurysm which appear to arise either by diapedesis of the red cells through the aneurysmal wall (Fig. 20) or by actual rupture of the aneurysm. This has already been demonstrated by Ballantyne and Friedenwald. In this series of cases examination of the retina mounted in a glass sphere showed both types of lesions scattered throughout the fundus but particularly aggregated in the posterior polar region. The anterior nasal area appears to be the least affected; in one of our cases, however, micro-aneurysms were evenly scattered throughout the whole fundus. Microscopical examination confirmed Ballantyne's report that they are situated mainly in the inner nuclear layer in the course of the capillaries which link the deeper and more superficial capillary plexus of the retina.

3. *Do micro-aneurysms occur elsewhere in the eye when diabetic retinopathy is present?*

In all cases in which diabetic retinopathy was present the iris, ciliary body and choroid were removed for examination by the methods previously described. After a prolonged search no definite micro-aneurysms were found in any of the preparations. No micro-aneurysms were found in the conjunctiva removed at post-mortem or in the biopsy specimen. From this small series of cases it is, therefore, legitimate to conclude that micro-aneurysms probably do not occur in the eye apart from the retina.

4. *Do micro-aneurysms occur elsewhere in the body when diabetic retinopathy is present?*

Examination of the cerebral vessels and of flat preparations of the omentum, peritoneum, pleura, pericardium, meninges, bladder wall, liver and renal capsules showed no evidence of micro-aneurysmal formation in any case, irrespective of whether

retinopathy was present or not. Serial paraffin sections of the organs removed at autopsy have not yet been studied but judging from the evidence so far obtained it would appear that micro-aneurysms do not occur in the vessels of the brain or serous membranes.

5. *What gives rise to micro-aneurysms and why are they confined to the retina?*

In attempting to explain the formation of micro-aneurysms in diabetic retinopathy, Ballantyne (1945) has suggested that they may result from the injurious effects of an unknown circulating chemical toxin, which is highly selective for the retinal capillaries. That such specific toxins exist is well known; Ballantyne draws an analogy with alloxan (mesoxalyl urea), which when administered to experimental animals destroys only the pancreatic islets (Dunn *et al*, 1943). The presence, however, of intercapillary glomerulosclerosis and other vascular lesions in diabetes, together with the frequently reported increase in capillary fragility, as measured by compression of the arm, indicate that the vascular disease is much more widespread and it would seem probable that the formation of aneurysms in the retina is simply an expression of this vascular degeneration brought about by mechanical factors peculiar, either to the retinal vessels themselves or to their immediate environment. Clinicians have often commented upon the engorgement of the retinal veins in diabetes and Michaelson and Campbell (1940), in a study of the anatomy of the finer retinal vessels, have pointed out that the deep plexus of vessels is a more closely-knit meshwork than the superficial one and that venous stasis is consequently most felt in these capillaries: it is in the deep plexus that the majority of micro-aneurysms occur. In other words it would appear that aneurysm formation is related to venous stasis and the peculiar structure of the retinal capillary network. The cause of the venous stasis is unknown. Hyperglycaemia of long duration is the important factor according to Elwyn, but Cristini and Tolomelli (1947) affirm that in the diabetic subject with retinitis there is frequently sclerosis of the larger pre-capillaries in the retina which brings about a condition of stasis with a resulting decrease of retinal arterial pressure and an increase of retinal venous pressure. The correct explanation, however, remains obscure.

Weinstein (1948) has suggested that haemorrhages in the diabetic fundus occur when dilatation of the retinal capillaries is associated with low ocular tension. It may be possible, therefore, that variations in ocular tension resulting from fluctuation in the blood sugar level may also be a factor in the formation of micro-aneurysms.

6. *What is the relationship of Kimmelsteil-Wilson's intercapillary glomerulosclerosis to diabetic retinopathy?*

In order to relate these two conditions it was first necessary to classify them in stages of severity. In deciding upon the presence or absence of intercapillary glomerulosclerosis, mild diffuse intercapillary thickening was neglected and only those sections showing definite globular or club-shaped masses of "hyaline" material in the glomerular tuft were considered positive and they were categorised as mild, moderate and severe according to the observer's impression of the degree and extent of the pathological change (Figs. 21 and 22).

The existing classifications of diabetic retinopathy refer to ophthalmoscopical appearances but minute aneurysms could be seen in the microscopical examination of the retina when the fundus appearances in life were normal. For the purpose of this investigation, therefore, the following grouping based upon Ballantyne's (1946) clinical classification was adopted :—

I. *Subclinical stage.* Where micro-aneurysms were found only on microscopical examination of the stained retina.

II. *Mild stage.* Changes chiefly in the central area; micro-aneurysms with or without punctate exudates.

III. *Moderate stage.* Dot and blot haemorrhages with confluent waxy exudates.

TABLE I

Case No.	Age	Sex	Known duration of diabetes in years	Retinopathy	K.W. disease	B.P. Systolic
1	52	M	25	0	0	150
3	72	M	4	0	0	160
5	59	F	—	0	0	190
7	75	M	35	I	0	170
8	12	F	1	0	0	—
9	63	F	13	II	Mild	85
10	67	M	14	I	0	—
11	73	F	—	0	0	100
12	75	F	—	I	0	160
13	68	F	—	0	0	—
14	73	F	5	III	Moderate	175
15	57	M	10	IV	Severe	210
16	60	F	3	I	Moderate	210
17	75	F	—	0	0	220
18	70	F	—	0	0	—
19	63	M	—	III	Mild	190
20	79	F	13	II	0	200
21	79	F	—	II	Severe	180
22	47	M	2 weeks	0	0	160
23	52	M	10	I	0	—
24	86	F	1 month	II	Severe	200

IV. *Severe stage.* Massive exudates and extensive retinal haemorrhages. Retinitis proliferans, detachment of the retina and vitreous haemorrhages.

As will be seen in Table I, retinopathy, as defined above, was present in 12 (57.12 per cent.) of the 21 cases examined and of these 7 (58.3 per cent.) showed Kimmelstiel-Wilson's disease of the kidney. The renal lesion was not found in any case where the retinal vessels were normal; the intercapillary glomerulosclerosis was always accompanied by retinal micro-aneurysms. Of the 5 cases of diabetic retinopathy in which the glomeruli were normal, 4 were subclinical and 1 was mild. The 3 more advanced forms of retinopathy were each associated with intercapillary glomerulosclerosis. This is too small a series of cases from which to draw conclusions of any great value but the implications appear to be that intercapillary glomerulosclerosis in the diabetic is regularly associated with retinal micro-aneurysms, whether they are detectable ophthalmoscopically or not, and that while retinopathy in the early stages may or may not be associated with the renal complication, the severe form is probably always associated with intercapillary glomerulosclerosis, but, when the two lesions co-exist, there is no correlation between their degrees of severity. These findings, as far as they go, are in accord with the report of Henderson *et al.* that advanced retinopathy is more or less regularly associated wth intercapillary glomerulosclerosis. Kimmelstiel and Porter found retinopathy in 86 per cent. of cases with the advanced renal lesion, but this percentage was based upon ophthalmoscopical appearances; it is probable that if it had been possible to examine the retinae microscopically a much higher figure would have been obtained. As stated above, microscopical or ophthalmoscopical retinopathy was present in 100 per cent. of our cases with intercapillary glomerulosclerosis, irrespective of the degree of severity of the glomerular involvement. It will be interesting to see whether this incidence is maintained in a larger series.

The problem of the aetiological relationship of the retinal and renal lesions is a less simple one, but after studying sections of intercapillary glomerulosclerosis and diabetic retinopathy side by side, it is difficult to resist the conclusion that one is dealing with manifestations of exactly the same pathological process modified by the different anatomical structures. In both there is localised capillary dilatation; in both there is localised degeneration and proliferation of the vessel wall. In one there is the formation of "hyalin" and in the other of "waxy exudates"; the chemical structure of neither is known and they may well be closely related. Allen's (1941) detailed studies of the glomerular lesion included

an attempt to assign definitive characteristics to the generic term "hyalin" by tryptic digestion and special staining; in the diabetic lesion he found resistance to tryptic digestion, affinity for aniline blue and marked argyophilia and lamination with silver stain. To this can be added the fact that this "hyalin" stains red with the Hotchkiss-McManus method. Apart from tryptic digestion, which we have not yet tried, all the above reactions may be demonstrated in the diabetic "waxy exudates" (Figs. 23 and 24). Frozen sections of the kidney and retina stained with acetic-carbol-sudan show that both the "hyalin" and "exudate" are intimately mixed with fat globules. Widespread difference of opinion exists among pathologists as to the exact site of the deposition of "hyalin" in the glomerulus; Kimmelstiel and Wilson claim that it is in the intercapillary connective tissue and Allen states that it is intramural. If we assume that there is, in fact, a close relationship between the retinal and renal lesions, a study of the retinal vessels in diabetes may throw some light on the problem. In the retina the vessels show a degeneration and proliferation of the vessel wall itself (Fig. 15) with the passage of "exudates" into the surrounding tissue. By analogy, therefore, it would seem possible that the hyalin in Kimmelstiel-Wilson's disease may be both intramural and intercapillary. Friedenwald suspects that the capillary dilatations associated with intercapillary glomerulosclerosis (Fig. 25) are also micro-aneurysms and on these grounds he brings the lesion into line with the retinopathy. Even if this were true, the presence of hyaline masses compressing the capillaries in the glomerulus, within the confines of Bowman's capsule, offers a purely mechanical explanation for the presence of localised capillary dilatations, which cannot apply in the retina, and it is doubtful whether the similarity of the lesions is more than superficial. Apart from this point, however, we are in complete agreement with Friedenwald's suggestion that both intercapillary glomerulosclerosis and diabetic retinopathy are manifestations of the same vascular process.

Redslob (1948) believes that it is impossible to distinguish ophthalmoscopically between diabetic and nephritic retinal lesions; the only difference he recognises is the absence of oedema in diabetic retinopathy and in his view, the two are analagous if not identical. Redslob feels that the answer to the problem of diabetic retinopathy is to be found in intercapillary glomerulosclerosis and he thinks it extremely probable that the renal lesion gives rise to the retinopathy. Our findings do not support this theory. A reference to Table I shows that no less than 5 of our cases had retinopathy without any evidence of glomerular involvement and this finding together with the fact that the more severe form

of retinopathy is regularly associated with intercapillary glomerulosclerosis suggests rather the reverse of Redslob's argument, *i.e.*, that the retinal disease precedes the renal lesion. That the development of intercapillary glomerulosclerosis may aggravate the retinopathy cannot be denied, however.

Thus the aetiology of both the renal and retinal lesions remains obscure and the elucidation of their exact relationship must await the solution of the larger problem of the cause and nature of the widespread vascular degeneration in the diabetic.

SUMMARY

Accumulated experience in pathological and clinical studies during the last few years points to a particular type of vascular degeneration in diabetes which is responsible for at least some of the more important complications of this disease. The evidence in the literature for this conclusion is briefly reviewed.

An investigation is being undertaken to compare the histopathological changes in the diabetic retina with disease in the vascular system generally and a preliminary report is given upon the examination of post-mortem material, including the eyes, from 21 diabetic patients.

The vessels of the retina, choroid, ciliary body, iris, conjunctiva, brain, meninges, pleura, pericardium, omentum, peritoneum, bladder mucosa and the capsules of the kidney and liver were examined by new methods of staining and preparation.

Ballantyne's report that the globular lesions on the retinal vessels are true capillary micro-aneurysms is confirmed and the methods employed have demonstrated further features in their morphology.

Micro-aneurysms were not found outside the retina, either in the eye, in the cerebral vessels or in the vessels of serous membranes, bladder wall or omentum. Their mode of origin is discussed and explanations for their localisation in the retina are advanced.

In each case the kidneys were examined for Kimmelstiel-Wilson's disease and the lesion was related and compared to the retinopathy. It is believed that intercapillary glomerulosclerosis and retinopathy are manifestations of the same pathological process modified by the different anatomical structure of the retinal and glomerular vessels.

The findings are not in accord with Redslob's belief that intercapillary glomerulosclerosis causes diabetic retinopathy. Early retinopathy can exist in the absence of intercapillary glomerulosclerosis and our investigation suggests that retinal changes probably precede the deposition of hyaline material in the glomerulus.

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CONTACT LENSES:
An analysis of the results of use*

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CONTACT Lenses were first fitted and worn in 1887, and since that time the literature of the subject has steadily increased. It has been extensively reviewed by Dallos (1936), Bruce (1937), Mann (1938), Darcy Williams (1946), Cross (1947), and others, and comprehensive text-books have been written by Dickinson and Hall, Treissman and Plaice, Obrig and other authors. Few reports have, however, been published giving detailed results of the use of contact lenses. Williamson-Noble (1938), Gyorffy, I. (1940), Gyorffy, S. (1944), Mann (1944), and Ridley (1946), have described results, but in each series the number of cases has been small and has not provided the full information which is so widely desired regarding tolerance to these optical aids, and the results of wear in different circumstances. It was decided, therefore, to conduct an investigation into the results of wearing contact lenses in a large number of patients, and, in addition to seeking information about tolerance, to inquire into various other aspects of the use of these appliances.

Scope of the investigation.

The co-operation was obtained of Messrs. Clement Clarke, Ltd., Messrs. Theodore Hamblin, Ltd., and Messrs. Davis Keeler, Ltd., and permission was obtained from all ophthalmic surgeons who had referred cases to these firms to send a questionnaire to their patients. Mr. K. Clifford Hall, F.S.M.C., also gave permission for a questionnaire to be sent to patients fitted by him. All patients who were fitted up to the end of 1945 have had a questionnaire sent to them which was made up as follows:—

CONTACT LENS REPORT

Name............	Age............
Address............	Date of fitting............
....	Ocular condition ....
Occupation............	Referred by............

Type of Contact Lens............

Time occupied in fitting of lens:

1. Number of sessions............
2. Time over which the sessions extended............

Dedicated to Professor J. Meller.

* Received for publication, March 24, 1949.

I. Do you, at the present time, wear your contact lenses? ....

II. If so:

(a) For what average periods are they worn? ....

1. Are they worn every day? ....
If not, for how many days a week? ....
2. What is the total number of hours they are worn per day? ....
3. What is the interval between periods of wearing them each day? ....
4. Are they worn at work? ....

(b) Why do you remove them? ....

1. Is there any discomfort? ....
2. Do you notice blurred vision while wearing the lenses? ....
If so, after how long of wearing the lenses, and is it equal in two eyes? ....
Does the blur persist after removal of the lens, and for how long? ....
If the lens is re-inserted immediately the blur clears, how long is it before it comes back? ....
3. Is there any other reason for removal? ....

(c) Do you put the lenses into the eye dry? ....
If not, what fluid do you use? ....
Do you feel that the period without blurring is influenced by the strength or composition of the solution used? ....

(d) Are you aware of air bubbles? ....
If so, are they a help or a source of trouble? ....

(e) What conditions do you find:
1. Most favourable for the wearing of contact lenses? ....
2. Least favourable? ....

(f) When reading with the contact lenses, do you have to wear spectacles also? ....

III. If you do not wear your contact lenses, why did you give them up? ....

IV. What benefits do you appreciate most in contact lenses, and in what respects have you been disappointed with them? ....

V. Knowing what you know now, would you go in for contact lenses again? ....

VI. How many times have the lenses been repolished? ....

VII. Additional comments, criticisms or suggestions ....

1,850 copies of the questionnaire were sent out and 875 replies were received. These replies have been analysed and the results determined. In some of the tables addition of the percentages does not make a total of 100. This is due to various questions having been left unanswered by some patients. The four fitters have been designated A, B, C and D. The methods of each varied slightly in different patients, but essentially Fitters A and B have fitted glass lenses from ocular moulds, with slight modification of the moulds; Fitter C has employed moulding with modification, or the modification of a selected shell, for the provision of glass lenses; while Fitter D has employed an extensive fitting set for providing standard lenses in glass or plastic, and

has carried out modification of these standard lenses where necessary. Where standard lenses were not suitable, Fitter D has used the method of taking moulds.

RESULTS

The analysis of the results will be reported in the order in which the questions appeared in the questionnaire. Some of the questions have been answered in an indefinite way, but this number is small, and the percentages of the results obtained from the examination of the replies should be significant. Every analysis of the results has not been possible, but those that appear the most instructive have been worked out.

1. *Occupation* (Table I).

Three per cent. of the total number worked in such occupations as singing, acting and dancing, which are usually regarded as an indication for the use of contact lenses. Sixty-two per cent. performed indoor occupations, mainly of a clerical nature, while 12

TABLE I

OCCUPATION

	Occupations where contact lenses are required for cosmetic reasons %	Other indoor occupations %	Other outdoor occupations %	Unoccupied or occupation not stated %
Total ...	3	62	12	23
Men ...	1	55	24	20
Women ...	6	68	1	25

per cent. were occupied in outdoor jobs. In the occupations where contact lenses were employed for cosmetic reasons, women favoured contact lenses six times as frequently as men.

2. *Ocular Conditions* (Table II).

It is demonstrated that more than half of the contact lenses ordered were in cases of myopia, and that the next two largest groups were mustard-gas keratitis and keratoconus. The mustard-gas keratitis cases were, of course, almost entirely male, while the numbers of women in the keratoconus and myopia groups were much higher than the men, because of the recognised feminine antipathy to spectacles. Contact lenses have been

TABLE II

OCULAR CONDITIONS FOR WHICH CONTACT LENSES WERE ORDERED

	Keratoconus %	Irregular astigmatism %	Myopia %	Hypermetropia %	High astigmatism %	Aphakia %	Mustard-gas keratitis %	Neuroparalytic keratitis %	Pemphigus %	Others %
Total ...	10	0.5	59	3	0.5	4	14	0.5	—	5.5
Men	3	0 5	46	3	1	5	29	0.5	—	8
Women ...	16	0.5	70	2	—	4	0.5	0.5	0 5	3
Younger than 30 years ...	5	1	80	3	—	2	—	—	—	6
31–50 years ...	14	—	53	2	1	5	14	1	—	6
Over 50 years	13	—	19	1	1	9	49	—	—	5

employed for myopia, especially in the young patients, while mustard-gas keratitis is confined largely to the older age groups, nearly all cases originating in the later years of the first world war. Patients suffering from other conditions are scattered more equally through all age groups, though both keratoconus and aphakia are slightly more frequent among the elderly.

3. *Age* (Table III).

It can be seen that very few contact lenses are ordered before the age of 18 years, and not many over the age of 60 years, and that the large majority are obtained before the age of 40 years, the peak period being between 20 years and 30 years. This is

TABLE III

THE AGE OF PATIENTS WHEN CONTACT LENSES WERE ORDERED

	Up to 18 yrs %	19–25 yrs. %	26–30 yrs. %	31–35 yrs. %	36–40 yrs. %	41–45 yrs. %	46–50 yrs. %	51–60 yrs. %	Over 60 yrs. %
Total ...	1	19	18	10	9	7	8	12	4
Men ...	1	16	15	7	7	4	14	20	6
Women ...	1	22	21	12	10	9	3	5	3

especially noticeable in the case of women, in whom 66 per cent. of all contact lenses are fitted on patients younger than 40 years, and 43 per cent. between 19 years and 30 years. The older age-groups contain more cases among the men, largely as a result of mustard-gas keratitis.

4. *Date of Fitting* (Table IV).

The patients who have replied to the questionnaire have nearly all been fitted within the last 10 years, only a small number having worn contact lenses longer than 6 years. The maximum

TABLE IV

THE NUMBER OF YEARS SINCE THE CONTACT LENSES WERE FITTED

	Up to 1 yr. %	1–2 yrs. %	2–3 yrs. %	3–4 yrs. %	4–5 yrs. %	5–10 yrs. %	More than 10 yrs. %
Total ...	8	22	17	10	8	20	1
Men ...	6	20	16	9	9	22	0.5
Women ...	9	24	17	12	8	18	1

number has been fitted during the past 2 years, but this period of wear is, it is considered, sufficiently long for patients to give a reasoned opinion of their reactions.

5. THE NUMBER OF SESSIONS (Table V).

It was considered that it would be instructive to find out the number of fitting sessions which had been employed to fit the lenses in each case, in order to ascertain whether or not this varied materially according to the results attained. It is interesting to note how the technique of the various fitters varies in this respect.

TABLE V

NUMBER OF SESSIONS EMPLOYED IN FITTING

	Up to 5 %	6–10 %	11–15 %	16–20 %	21–30 %	31–40 %	41–50 %	51–60 %	Over 60 %
Total ...	11	17	12	10	10	3	2	1	1
FITTERS									
A ...	5	9	5	9	18	18	5	—	9
B ...	31	58	3	1	1	—	—	—	—
C ...	2	12	18	15	15	3	2	1	1
D ...	36	—	—	—	—	—	—	—	64 did not answer

The time employed in fitting is a matter of extreme importance, because the expense of the lenses is intimately connected with this factor, and contact lenses for the masses cannot become an accomplished fact until the fitting-time can be reduced to a minimum. It is interesting to note that Fitter D usually fits in less than five sessions, and that Fitter B rarely employs more than ten. The other two require longer periods.

6. *Tolerance* (Tables VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV).

The most important aspect of the use of contact lenses concerns their tolerance, and it was to obtain some authoritative information on this matter that this investigation was primarily undertaken. Table VI indicates that of all the people who have answered the questionnaire, 875 in number, 33 *per cent. have given up using their lenses*. This emphasizes the great responsibility which rests upon anyone who orders or fits contact lenses,

TABLE VI

THE PERCENTAGE OF PATIENTS WHO ARE WEARING THEIR CONTACT LENSES AT PRESENT

	Yes %	No %	Occasionally Sometimes %	One eye only %
Total	55	33	9	3
Men	49	38	9	4
Women	61	28	10	1
Up to 30 yrs. of age	60	30	9	1
31–50 yrs of age ...	49	34	13	4
Over 50 yrs of age	68	21	5	5
FITTERS				
A	35	42	19	4
B	56	34	8	2
C	58	30	9	3
D	57	33	9	1

because there is no doubt that efficient selection of patients should lower this figure considerably. Men have defaulted more frequently than women, possibly because of the greater determination of the latter to succeed for cosmetic reasons. The over-50-years age-group also shows a significantly lower number of non-wearers, which may be the result of the number of the mustard-gas keratitis cases in this section. There is no great difference in the results of the different fitters, the failures of whom vary between 42 per cent. and 30 per cent. Those persons who are still wearing their contact lenses were further questioned to ascertain the average periods for which they can be worn (Table VII). About one-third can wear them for eight hours or more, and only 16 per cent. for less than four hours. There is no marked difference between men and women, but the group over 50 years shows a higher percentage than the others who wear them for eight hours or more. Fitter B shows a lower number than the

TABLE VII

THE AVERAGE PERIODS (IN HOURS) FOR WHICH CONTACT LENSES ARE WORN, AMONGST PATIENTS WHO ARE STILL WEARING THEM

	One %	Two %	Three %	Four %	Five %	Six %	Seven %	Eight %	More than 8 hours to all day %	Variable %
Total ...	1	7	8	18	7	4	2	2	30	18
Men	0.5	7.5	7	20	7.5	3 5	3	3	33	12
Women ...	1	6	10	16	6	4	1	2	27	23
Up to 30 years of age ...	2	6	11	15	8	4	3	3	30	17
31-50 years ...	1	9	9	18	8	4	1	4	24	16
Over 50 years	—	4	3	16	5	4	1	—	40	24
FITTERS										
A	—	—	5	27	9	5	—	5	27	18
B	3	9	20	15	3	3	—	3	14	30
C	1	5	5	17	8	4	3	3	32	18
D	2	16	15	13	4	3	2	2	30	10

average who can wear their lenses for eight hours or more. This fitter shows a large number of patients who state that they wear their lenses for varying times, possibly for special social occasions, etc., but it is unlikely that many of them would be as long as eight hours. The majority of people who wear contact lenses wear them every day (Table VIII). Some people, however, wear their lenses for more than one period in each day,

TABLE VIII

THE PERCENTAGE OF PERSONS WHO WEAR THEIR CONTACT LENSES EVERY DAY

	Yes %	No %	Usually %
Total ..	75	16	9
Men ...	74	18	8
Women ...	76	14	9

and the record of the total number of hours in which they are worn in the day differs from the record of the number of hours for which they can be worn at one time (Table IX). Fifty-eight per cent. of the wearers use their lenses for eight hours or more

Table IX.

TOTAL NUMBER OF HOURS THE LENSES ARE WORN EACH DAY

	One %	Two %	Three %	Four %	Five %	Six %	Seven %	Eight %	More than eight hrs %	Variable %
Total... ...	1	2	2	7	3	4	1	11	47	18
Men	0.5	3	2	5	4	5 5	1	13	49	13
Women ...	1	2	3	8	3	3	1	8	45	22
Up to 30 yrs.	2	2	3	6	2	4	2	8	51	18
31–50 yrs. ...	1	3	3	7	4	4	1	13	41	19
Over 50 yrs....	—	3	1	4	4	4	3	6	50	19
FITTERS										
A	5	—	—	—	—	—	—	9	72	9
B	2	2	3	9	10	6	1	9	29	29
C	1	2	1	5	3	4	2	12	47	18
D	—	7.5	7.5	12	—	3	—	3	54	12

in the day. There is no significant difference as between men and women or in the different age groups, but the various fitters show different results. Fitter A has 81 per cent. of his patients who still wear the lenses for eight hours or more a day, while only 38 per cent. of Fitter B's patients wear them for this period. It will be remembered that Fitter A, in spite of this successful tolerance, showed the highest percentages of failures. The

Table X

INTERVAL BETWEEN PERIODS OF WEARING

	Less than 1 hr. %	1 hr. %	2 hrs. %	3 hrs. %	More than 3 hrs. %	Variable %	Only worn once per day %	Long enough to change fluid %
Total	8	13	11	4	6	11	33	4
Men	9	16	12	2	6	8	33	5
Women	8	11	11	5	6	14	32	2
Up to 30 yrs. ...	10	15	12	2	7	12	31	3
31–50 yrs.	6	11	14	5	5	12	33	5
Over 50 yrs. ...	8	14	12	1	6	6	32	5
FITTERS								
A	22	9	5	14	9	5	27	—
B	9	17	15	4	8	23	21	3
C	6	12	12	4	5	9	39	3
D	12	20	9	—	6	10	21	6

majority of patients who change their lenses favour an interval of about an hour between the periods of wear, though some prefer longer (Table X). A larger proportion of Fitter C's patients than those of the other fitters seem to use their lenses for one session only in the day.

Investigations were made into the number of patients suffering from keratoconus, myopia, aphakia, and mustard-gas keratitis who had given up wearing their lenses (Table XI). There were not sufficient cases of other pathological conditions to allow

TABLE XI

PERCENTAGE OF PATIENTS STILL WEARING THEIR CONTACT LENSES IN CERTAIN PATHOLOGICAL CONDITIONS

	Yes	No	Occasionally Sometimes	One eye only
	%	%	%	%
Keratoconus	74	15	5	6
Myopia...	51	37	11	1
Aphakia	46	32.5	15	6.5
Mustard Gas Keratitis	77	12	5	6

significant results. Fewer patients than the average had given up wearing their contact lenses among those with keratoconus and myopia, whereas among the purely myopic patients the number who are no longer wearing them is above the average. It was a surprise to realise that the percentage of aphakic persons wearing their contact lenses were even less than the myopes. It appears that though a contact lens reduces the size of the image in the aphakic eye and overcomes the prismatic effects of a strong

TABLE XII

AVERAGE PERIODS FOR WHICH LENSES ARE WORN IN VARIOUS PATHOLOGICAL CONDITIONS

	One hr.	Two hrs	Three hrs.	Four hrs.	Five hrs.	Six hrs.	Sever hrs.	Eight hrs	More than Eight hrs.	Variable
	%	%	%	%	%	%	%	%	%	%
Keratoconus...	—	—	4	9	2	2	—	2	37	31
Myopia ...	2	7	10	18	7	5	2	3	26	18
Aphakia ...	—	9	5	5	—	—	5	—	38	24
Mustard-Gas Keratitis	—	8	8	23	9	3	1	—	34	—

convex lens, this is not sufficient to allow fusion of images and comfortable vision in a very large proportion of cases. This is probably the result of absence of accommodation in the aphakic eye.

It was shown that, among those still wearing them, the lenses were worn for significantly longer periods in keratoconus, aphakia and mustard-gas keratitis than in myopia, where the reward was not so great (Table XII). The lenses were worn nearly every day in over 80 per cent. of cases of keratoconus, myopia and mustard-gas keratitis, but the aphakics did not seem to make such constant use of them (Table XIII). The lenses were worn for a longer total time in the day if the wearing hours

TABLE XIII

WHETHER THE LENSES ARE WORN EVERY DAY IN VARIOUS PATHOLOGICAL CONDITIONS

	Yes %	No %	Usually %
Keratoconus	83	9	6
Myopia	73	18	9
Aphakia	62	33	—
Mustard-Gas Keratitis	74	12	14

were divided into two periods than if single sessions were employed, about 55 per cent. of cases of keratoconus, myopia and aphakia being able to wear them for eight hours or more, while

TABLE XIV

NUMBER OF HOURS THE LENSES ARE WORN PER DAY, ACCORDING TO PATHOLOGICAL CONDITION

	One %	Two %	Three %	Four %	Five %	Six %	Seven %	Eight %	More than eight hrs. %	Variable %
Keratoconus...	—	—	—	4	—	2	2	4	51	26
Myopia ...	1	2	3	7	4	4.5	1.5	9	46	20
Aphakia ...	—	5	5	9	—	—	5	9	43	19
Mustard-Gas Keratitis	—	3	1.5	1.5	3	6	—	19	57	6

76 per cent. of cases of mustard-gas keratitis had a tolerance of eight hours or more in the day (Table XIV). The majority of these patients who wear their lenses for two sessions in the day allow an interval of about one hour (Table XV).

TABLE XV

INTERVAL BETWEEN PERIODS OF WEARING LENSES ACCORDING TO PATHOLOGICAL CONDITION

	Less than 1 hour	1 hour	2 hours	3 hours	More than 3 hours	Variable
	%	%	%	%	%	%
Keratoconus	8	20	9	2	—	7
Myopia...	12	13	13	4	6	13
Aphakia	5	14	—	—	—	14
Mustard-Gas Keratitis	18	15	12	5	11	3

It is natural that most people endeavour to wear their lenses both at work and during their social activities. It is demonstrated that only a very small proportion of contact lens wearers do not use their glasses at work (Table XVI), and consideration must be given to the question of whether it is justifiable to order contact lenses to be worn only for social activities.

TABLE XVI

PERCENTAGE OF CASES WHO WEAR THE LENSES AT WORK

	Yes	No	Sometimes
	%	%	%
Total	72	15	8
Men	72	14	8
Women	73	16	7
Up to 30 yrs. of age	69	19	9
31–50 yrs.	76	14	8
Over 50 yrs. ...	71	5	6

9. *Why are the Contact Lenses removed?*

The patients who answered this question gave a variety of answers. Thirty-nine per cent. stated that the contact lenses were removed because they noticed veiling, blurring, and fading vision, or a mist around lights; the problem of Sattler's veil which has persisted since contact lenses were first used is thus demonstrated as being the greatest obstacle to their continuous use. Thirty per cent. removed the lenses on account of pain, irritation, smarting, discomfort and watering, while 18 per cent. only removed them for cleaning, renewing the lotion and removing eyelashes. Smaller numbers have stated that they remove them on account of tiredness, nervous tension, or for a rest, and a few find difficulty in removing them if they remain in too long, or

they say that their lens fits badly. Bubbles necessitate removal in some cases. The analysis of the various groups demonstrates that veiling appears to be more common in the age group below 30 years, and that Fitter B and Fitter D appear to have a higher percentage of veiling than the other groups. Fitter A shows a low percentage of irritation but a higher number of cases who remove their lenses on account of bubbles than the other fitters.

10. *Is there any discomfort?* (Table XVII).

A small number of people gave an unequivocal affirmative to this question. Rather more gave a firm negative. Nearly half preferred to be indefinite and returned the answer that they sometimes had slight discomfort. It must be noted that in this question Fitter A showed a significantly smaller number of persons who admitted discomfort than the other fitters, which agrees with the finding that a large number of his patients were able to wear the lenses for long periods.

TABLE XVII

THE PERCENTAGE OF THOSE WHO ADMIT DISCOMFORT

	Yes %	No %	Sometimes %
Total	24	32	42
Men	21	32	45
Women ...	27	31	40
FITTERS			
A	14	41	41
B	29	35	33
C	25	27	46
D ...	22	40	36

11. *Blurred vision when wearing the lenses* (Table XVIII).

Blurring of vision while wearing contact lenses is due, in the majority of cases, to that oedema of the corneal epithelium which has been termed Sattler's veil. The answers reveal that 74 per cent. of patients are embarrassed by onset of blurring of vision after wearing their lenses for a variable period. Two per cent. admitted that this happened only when the contact lenses needed cleaning, or when the fluid required changing, while 2 per cent. found that blurring only occurred in a hot atmosphere or with fatigue. In these latter groups it is probable that the blurring was not due to a Sattler's veil but to mucus or other deposits on the lenses. Dimness of vision due to bubbles was specifically mentioned in 0·5 per cent. of cases.

TABLE XVIII

THE PERCENTAGE OCCURRENCE AND CAUSE OF BLURRING OF VISION

	Yes	No	Due to bubbles	Dirty lens or fluid	Hot atmosphere with fatigue
	%	%	%	%	%
Total	74	20	0.5	2	2
Men	76	18	0.5	2	1.5
Women ..	74	21	—	1	2
Up to 30 yrs. ...	76.5	18	0.5	2	2
31-50 yrs. ...	72	23	—	1	1
Over 50 yrs. ...	75	17	—	2	3
FITTERS					
A	87	9	—	4	—
B	85	7	—	3	3
C	72	22	—	1	3
D	79	19	—	—	—

There is no significant difference in the incidence of blurred vision between men and women or in the different age groups, but Fitter A and Fitter B appear to have a higher incidence than Fitter C and Fitter D. It should be emphasized that none of these patients had been fitted with perforated or grooved lenses, which have materially changed the frequency with which veiling occurs.

The onset of veiling occurs after varying periods of wear, but it commonly tends to happen after three or four hours. No

TABLE XIX

LENGTH OF TIME DURING WHICH CONTACT LENSES ARE WORN BEFORE VEILING OCCURS, IN CASES WHICH VEIL

	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	6-8 hours	Over 8 hrs	Variable
	%	%	%	%	%	%	%	%	%
Total	4	11	14	13	7	7	3	5	20
Men	5	7	14	16	9	4	3	7	18
Women	3	15	14	10	5	8	3	4	22
Up to 30 years ...	4	10	12	13	11	7	5	7	21
31-50 years . ..	5	15	17	13	6	5	2	2	22
Over 50 years ..	4	6	8	14	3	6	1	8	15
FITTERS									
A	—	—	10	35	10	10	—	5	25
B	7	23	24	3	3	5	3	—	25
C	4	7	9	13	8	6	4	6	20
D	2	18	24	17	6	7	2	4	18

important difference is present in the different age groups or between men and women, but there seems to be a difference between the different fitters. Fitter A and Fitter C show a peak at four hours, while Fitter B and Fitter D show their peak at the three-hour period. It is significant that only in 5 per cent. does veiling occur after periods of more than eight hours.

A material percentage show that there is a variation in the amount of veiling in the two eyes. This may indicate that variation in fitting is a factor. It is worthy of note that the two fitters whose patients show the peak of veiling at four hours seem to show a higher relative number who notice a difference in veiling between the two eyes.

TABLE XX

IS BLURRING EQUAL IN BOTH EYES?

	Yes %	No %	One lens only worn %
Total	40	28	10
Men	34	36	13
Women ...	45	22	8
Up to 30 yrs. ...	47	31	5
31–50 yrs. ...	35	26	13
Over 50 yrs. ...	24	35	15
FITTERS			
A	50	35	—
B	51	11	13
C	33	30	13
D	58	33	—

TABLE XXI

PERSISTENCE OF "BLURRING" AFTER REMOVAL OF LENS

	No persistence %	Less than 15 mins. %	15–30 mins. %	31–45 mins. %	46–60 mins. %	More than 1 hr. %	All the time %	Variable %
Total	—	23	23	5	10	8	1	11
Men	—	16	21	6	15	11	2	11
Women ...	—	29	25	3	6	6	—	11
Up to 30 yrs....	—	28	27	3	10	7	—	13
31–50 yrs. ...	—	24	24	7	10	7	2	8
Over 50 yrs. ...	—	17	12	3	9	12	4	9
FITTERS								
A	—	15	40	—	—	5	—	35
B	—	42	21	5	5	2	—	15
C	—	20	19	5	10	12	2	10
D	—	13	37	4	18	4	—	2

TABLE XXII

RECURRENCE OF VEILING AFTER REINSERTION

	Up to half-hour %	Half-hour–1 hour %	1 hour %	2 hours %	3 hours %	4 hours %	5 hours %	6 hours %	More than 6 hours %	Variable %
Total	6	4	5	10	6	6	2	1	2	9
Men	5	5	6	8	9	7	4	2	2	11
Women ...	8	2	5	11	4	5	1	—	1	7
Up to 30 years	6	5	5	10	10	7	3	1	3	6
31-50 years ...	6	2	7	13	5	6	3	1	1	5
Over 50 years	5	3	1	4	4	3	—	—	—	20
FITTERS										
A	10	—	10	10	—	10	—	—	—	25
B	8	5	12	20	3	2	—	—	—	8
C	5	3	4	6	5	6	3	—	1	10
D	9	7	4	15	17	9	4	4	4	—

Veiling takes place more rapidly following reinsertion of the lenses after clearing of a veil than when they are inserted for the first time in the day. There is no significant difference between the sexes or between the age groups, but the figures for the different fitters show that whereas Fitter A, Fitter B and Fitter D show a peak in their series at about two hours, the Fitter C series shows fairly equal figures up to four hours' wear.

Questioning indicated that after a second insertion veiling was the usual cause of subsequent removal, though 27 per cent. removed them because of irritation, smarting, discomfort and watering.

Fluid with which the lens is inserted.

Of the total persons using contact lenses at present 39 per cent. put them into the eye dry. Of this number the large proportion are fitted by one fitter, of whose patients 56 per cent. insert the lenses dry, while 44 per cent. use some fluid. Of the other fitters' patients only 2-4 per cent. insert the lenses without fluid of some kind. The fluid most commonly used was normal saline—by about 73 per cent. of all who did not insert the lenses dry. The remainder used 2 per cent. or 2½ per cent. sodium bicarbonate solution, cold water, warm water, distilled water, boric acid solution, Optrex, various buffer solutions, and, in a few cases, saliva. The patients were asked to state whether the period of veiling was affected by the type of fluid. 25 per cent. thought it was, and 25 per cent.

TABLE XXIII

DOES THE FLUID AFFECT THE VEILING?

	Yes	No	Doubtful or no reply
Total	25%	25%	50%
FITTERS			
A	25	45	30
B	46	24	30
C	9	23	68
D	72	24	4

thought it was not. The remaining 50 per cent. either did not answer the question or gave indefinite replies. No significant difference was apparent between the sexes or in different age groups, but the results of the various fitters show marked differences. The majority of patients of Fitter A and Fitter C did not consider that fluids affected the veiling, whereas the majority of the patients of Fitter B and Fitter D considered that the influence of fluid upon veiling was considerable. Several patients emphasized that they felt that sodium bicarbonate solution helped to prevent veiling, and that veiling was more common if the solution was not fresh. It may be that in this matter the patients tend to reflect the views of their fitters.

The influence of air bubbles.

Enquiry was made to ascertain whether or not the formation of air bubbles was a serious factor in the wearing of contact lenses.

TABLE XXIV

DO AIR-BUBBLES FORM WHEN CONTACT LENSES ARE WORN?

	Yes %	No %	Sometimes %
Total... ...	44	19	36
Men	50	19	30
Women	39	19	42
Up to 30 yrs. ..	43	21	36
31–50 yrs	42	19	38
Over 50 yrs. ...	50	16	33
FITTERS			
A	18	18	64
B	35	17	48
C	47	20	32
D	44	21	34

Table XXIV shows the results. The essential fact is that only about 20 per cent. of cases do not suffer from bubbles at times, and this seems to be constant in both sexes, at all ages, and with any fitter.

Those persons who suffer from bubbles while wearing contact lenses do not all find them a hindrance. A small proportion find them a help, and some do not consider them an embarrassment.

TABLE XXV

EFFECTS OF AIR BUBBLES

	Those affected regularly by bubbles %	Those affected sometimes by bubbles %
Bubbles give no trouble	9	17
Bubbles a help	10	7
Bubbles cause great trouble	56	46
Bubbles cause slight trouble	23	23

This feature is of some interest in that veiling appears to be less marked when a bubble is present, and those people who can tolerate a bubble without discomfort may be relieved of the greater trouble of blurring of vision.

Most and Least favourable conditions.

Questions were asked to elicit the most favourable and least favourable conditions for wearing contact lenses and this provided a multitude of replies, many of which were completely contradictory. It is not felt that any useful purpose would be served by analysing these answers but some report of them may prove helpful to the providers and wearers of contact lenses.

Some persons find contact lenses comfortable at all times, and others find them to be uncomfortable always. Most people find the ideal conditions to be moderate sunlight or soft artificial light, and state that strong sunlight and bright artificial light may produce discomfort. Bluish fluorescent lighting is also criticized by some wearers and defective illumination may cause discomfort. Cool weather, dry cold weather, dull days, and rainy days all find their adherents, but windy weather whether dry or humid, causes trouble to some people. Some persons are happier in the morning, and others in the evening. It may be interesting to flying personnel to know that the strong light that is present above the clouds causes intolerance with some persons. There seems

no doubt that clean dry non-dusty rooms without smoke in the atmosphere are much more comfortable for wearers of contact lenses than hot, dusty, smoky places. People with contact lenses often dislike seats near the fire, while cinemas and crowded restaurants are likewise sources of discomfort. The psychological aspect of contact lenses is stressed in the observation by some persons that contact lenses can be worn more easily when they are alone than when they are in company, while having " nothing to do " or having to " look about " cause difficulty in other subjects. Sleeping is an unsuitable pastime when wearing contact lenses, and many people say that they are at their best when they are relaxed and the eyes are not tired. Some patients consider the lenses to be ideal for use in the open air, and especially for open-air sports and exercise, while some prefer them for indoor sports and dancing. Some like to use contact lenses for close work, while others feel that they are less suitable for this occupation than for distance. Many housewives find contact lenses ideal for general use while doing their housework. Mild degrees of ill-health such as colds in the head seem to have a detrimental effect upon tolerance to contact lenses. It appears, therefore, that there are few absolute contra-indications for contact lenses, but that hot, dusty, smoky atmospheres reduce tolerance in a large number of wearers, and that they find their most satisfactory use in the open air in a temperate climate.

TABLE XXVI

PERSONS WEARING ADDITIONAL SPECTACLES

	Yes %	No %	Remove Contact Lens for reading %
Total	22	75	1
Men	34	61	1
Women ...	12	86	1
Up to 30 yrs. ...	3	96	1
31-50 yrs. ...	16	81	1
Over 50 yrs. ...	76	13	4

Wearing of additional spectacles.

Contact lenses are normally fitted for distance wear. It is unusual for patients to have a special pair for reading, owing to the difficulties of changing them, and the bifocal contact lens is not yet a practical proposition. Presbyopic patients find it most convenient to wear a reading addition in spectacles. Table XXVI

indicates the numbers of people who have to do this and illustrates the large number of people who do it among the elderly age groups, and also the natural distaste of women for spectacles.

Why were contact lenses given up?

It was considered that it would be useful to learn from those patients who have given them up the reasons for discontinuing their wear. The numbers giving different reasons are small, and it does not appear that the percentages of the different groups would be of statistical value.

Some people asserted that the lenses did not fit, but this can only be a statement of opinion, since in the opinion of the fitters they did fit or they would not have been supplied. Allied to this reason is the extreme discomfort claimed by some wearers, and the early onset of veiling which worried others. Persistent redness of the eyes (termed conjunctivitis) caused some patients to stop using their lenses. Some wearers who obtained them for use only in games, found that they were too much of a nuisance, and gradually ceased to use them, while others found discomfort with close work and similarly gave them up. General inconvenience and uncertainty regarding the length of time they could be worn caused some people to cease using them. A number of reasons given for the failure to continue wearing contact lenses seem to reveal lack of will to wear them. "Difficulty in finding opportunity for removal and reinsertion," "difficulty" or "nervousness" in inserting and removing the lenses, and finding that the lenses were "unsuitable for the optical condition." Other reasons seem to fall within the group of pure excuses with very little reasonable foundation. "No time to persevere and get used to them," "they seemed to be harming my eyes" and "they caused restriction of movement of the eyes" do not seem to offer a sound basis for giving up the lenses. Losing the lenses or breaking them and being unable to afford the expense of replacement seems a more reasonable excuse, even if it illustrates gross carelessness. Inability to get the lenses refitted or repolished suggests, again, an absence of keenness. A final group complained of difficulties with the fluid used, and this also does not appear to be a valid excuse. Suitable co-operation between the fitters and wearers should eliminate this whole group.

A study of the reasons advanced for giving up contact lenses confirms the orthodox opinion that for success in wearing these appliances there must be a *real* desire on the part of the patient to make them a success. In this respect a great responsibility rests on the ophthalmologist only to advise contact lenses for

people who have the correct mental approach to the difficulties involved. These difficulties should be exaggerated rather than underestimated at the initial examination.

Benefits of contact lenses.

Patients were asked to give their ideas of the benefits of contact lenses, and though the answers produce little that is new, they are of interest in providing the considered opinion of persons who have devoted considerable time and trouble to being fitted with, and wearing contact lenses.

Many people appreciate being able to avoid wearing spectacles, some for reasons of vanity or because they consider their appearance to be thereby enhanced. Some claim greater comfort with contact lenses, and others an increase of self-confidence. The wider field of vision is appreciated by some wearers, and is partly attributable to the fact that the lens moves with the eye. High myopes notice the absence of light reflections, in addition to their improved vision, while people with irregular astigmatism and conical corneae are impressed by the enormous visual improvement which occurs. A benefit which seems to have little solid foundation, though noted by a few patients, is that the lenses help to keep the eyelids open. The benefit of these optical aids in sports, such as swimming and hunting, is mentioned by several observers, and their advantages for actors and musicians are also stressed. The fact that the transparency of these lenses is not affected by rain, spray, sweat, or other moisture is a well-recognised feature which receives constant reinforcement.

Disappointments in Contact Lens wear.

The statements of patients regarding the points in which contact lenses have proved disappointing are interesting, and may be of value to contact lens workers when advising possible wearers in the future. Many of the disappointments are relative in type, and could perhaps have been avoided by more detailed advice before fitting was begun. There is some overlap between this group and that in which patients gave their reasons for discarding their lenses, and it appears that if the disappointment was too great, further wear was suspended.

Some people were disappointed that they could not wear the lenses the whole time, or that they could not wear them for longer periods, while others were disillusioned at the long time it took to get used to them. Persistent blurring was the cause of intolerance and disappointment in many cases. General discomfort, inconvenience and nuisance caused some disappointment, while other

people noticed aching with close work, or had hoped that the general vision would be better. The reddening of the eyes, and the intolerance to glare and bright sunshine, disappointed many people, while some people were annoyed to find that the glasses caused discomfort in enclosed smoky atmospheres and could not therefore be worn at dances. Some people were disappointed that the lenses could not be worn comfortably for sport as had been anticipated.

Would you go in for contact lenses again?

This question was asked in the full knowledge that a large number of patients could not be expected to admit that they had made an error of judgment, and would state that they would certainly be prepared to try them again. Table XXVII shows that the results were almost unanimous in the opinion that they would be prepared to go in for them again. There were, however, certain

TABLE XXVII

WOULD YOU GO IN FOR CONTACT LENSES AGAIN?

	Yes	Doubtful	No	If fitting were improved	Not if spectacles gave same vision	If contact lenses were improved	If cheaper	Not for continuous wear	If can be used without lotion
	%	%	%	%	%	%	%	%	%
Total ...	88	5	3	—	0.5	—	1	1	—
Men ...	87	4	2	0.5	0.5	—	2	1	—
Women ...	89	5	3	—	0.5	0.5	—	0.5	0.5
Up to 30 years .	90	4	3	—	0.5	—	0.5	2	—
31-50 years ...	86	6	2	—	—	1	2	1	—
Over 50 years ..	89	3	1	1	—	—	—	—	—
FITTERS									
A ...	88	4	4	—	—	—	—	—	—
B	86	3	4	—	2	—	—	2	2
C	90	5	2	—	—	—	1	1	—
D	84	9	4	—	—	—	3	—	—

qualifications which should be mentioned. Some feel that the fitting could be better, or that they would not have the lenses again unless they were improved, or unless blurring and discomfort are eliminated. Some people feel that the lenses should be cheaper before they would go in for them again, and others that they would not have them again unless they could be used without lotion. A proportion of people think that contact lenses are a failure for continuous wear, but that they are useful for special purposes such as dancing, acting, etc.

Repolishing of lenses.

The questionnaire ended with an enquiry regarding the number of times the lenses had been repolished. This simple procedure increases the comfort with which the lenses can be worn and should normally be carried out about every 2 years. Table XVIII shows that more than half the patients had never had their lenses repolished. This figure is largely due to the fact that many of the patients had only been wearing their lenses for a year or less. It is noteworthy that the age-group showing the highest percentage of repolishing was the group "over 50 years," many of whom had worn their contact lenses for the longest time.

TABLE XXVIII

REPOLISHING OF LENSES

	Once %	Twice %	Three times %	Four times %	Five times %	Six times %	Seven times or more %	Never %
Total	21	7	4	1	—	1	4	58
Men	23	4.5	2	3	—	1	3.5	59
Women	19	8.5	5	0.5	1	1	4	57
Up to 30 yrs.	19	5	4	0.5	0.5	0.5	2.5	65
31–50 yrs.	18	8	3	2	1	1	6	57
Over 50 yrs.	35	4	3	2	—	3	5	44

Contact lenses among Flying Personnel in the R.A.F.

Through the kind co-operation of Air Marshal P. C. Livingston, C.B., C.B.E., Director-General, R.A.F. Medical Services, and of Air Commodore J. C. Neely, Consultant in Ophthalmology, R.A.F., I have been allowed to examine the records of flying personnel who were fitted with contact lenses during the second world war. Their records show that 31 flying members of the R.A.F. were fitted with contact lenses. Most of them were pilots, but a few navigators and air gunners were in the number. Two of these men had unilateral aphakia, and the remainder suffered from defective vision due to myopia, myopic astigmatism, mixed astigmatism or hypermetropic astigmatism. The aphakic patients were pilots who had had traumatic cataract. One found his lens entirely satisfactory, and he flew 350 hours while wearing it, in single-seater fighters, and noticed no diplopia, while his judgment in flying was unimpaired. The other was able to wear his contact lens for 4 hours at a time before soreness

compelled its removal, but while wearing it he noticed diplopia for distant vision, and so flying was not possible.

Consideration of the men who wore contact lenses for visual defect reveals that in all cases where they were fitted, flying judgment and observation were unimpaired. More detailed analysis of the flying records reveals that 14 cases of the 29, just under 50 per cent., may be regarded as satisfactory. These men were able to take their full part in flying duties with unimpaired visual acuity. Certain observations are made by some of these cases which may be recorded. One noted that though he could fly in comfort in his lenses for up to 6 hours, his tolerance was reduced to 2 hours if he wore them in the house. One noticed slight discomfort from glare while he was training overseas. Another noticed slight irritation from fumes in the cockpit, and one pointed out the advantage of being able to fly in an open cockpit with contact lenses, without using goggles. This series contained a well-known fighter pilot, who had about 2 dioptres of myopia in each eye. He completed over 1,000 hours of flying, including 600 hours on operations, wearing his contact lenses, and won the D.S.O. and D.F.C. He could wear his contact lenses for up to 24 hours at a time.

The remaining 15 cases included one who was completely unsatisfactory. He never achieved more than one hour of tolerance, and was never able to fly with his contact lenses. The other 14 may be regarded as modified successes. Ten of them wore the lenses for flying and found them fully successful, so far as vision and visual judgment were concerned, but their tolerance was so reduced by veiling, that they could never become quite visually efficient. Three found that they could fly with the lenses perfectly well, but that heat and glare caused discomfort. One of these, a pilot in a Fighter Squadron, had to spend considerable spells in readiness for flying and be prepared to rush to his aircraft within seconds of receiving an alert. His tolerance was not very great, and long spells of "readiness" causes difficulty. Another pilot who flew many hours with contact lenses complained that they caused a sensation of weight in the eyes, and he also stated that when he pulled out of a power-dive he felt as though the lenses were being dragged out on to his cheek. A pilot who was wearing contact lenses was involved in a crash, and broke the goggles he was wearing, but his contact lenses were undamaged.

The records of this fairly small series of cases show that contact lenses can be employed for flying purposes by some persons, and that the difficulties which arise are the same as with other wearers, and associated especially with defective tolerance. Under present

circumstances they may be regarded as a possible assistance in keeping a trained man on flying duties, but probably not worth consideration for recruits.

CONCLUSIONS.

Contact lenses have been used for more than fifty years, and at the present time are being worn by rapidly increasing numbers of patients. Many are attracted to them by the thrill of using some new instrument, and some because they have an antagonism to spectacles which is almost pathological. These analysed results indicate that they are not entirely satisfactory as optical appliances. One-third of all the patients who answered this questionnaire have ceased to wear their lenses, although among those who wear them for pathological states of the eye this percentage is lower. Those persons who continue to wear their lenses may not be able to tolerate them for more than one or two hours a day, though the majority can use them for longer periods. The results obtained by some fitters are better than those of others, though the differences are not as great as might have been expected, and the satisfaction of the patients seems greater in some respects with one fitter, and some respects with another. There seems no doubt that the mental attitude of the patient to his lenses is an important factor, and it is most important that the greatest care should be taken in selecting patients who are suitable subjects, in order that the number of failures may be reduced to the lowest possible number. A survey of the use of contact lenses by the Royal Air Force indicates that here, as among civilians, the results were not uniformly satisfactory. In spite of the great amount of work which has been carried out on contact lenses, it appears that satisfactory fitting is still the major problem, and that, as improvements proceed in the technique, so will tolerance increase.

SUMMARY.

An analysis of the answers of 875 contact lens wearers to a questionnaire provides information upon the fitting of contact lenses, upon the indications for their use, and upon the problem of tolerance. The different aspects of tolerance are investigated, and the opinions of the wearers on the benefits and disadvantages of contact lenses are reported. It is shown that, of this series, one-third of the total number of persons fitted with contact lenses had ceased to wear them, and the various causes are discussed. A report is given of the use of contact lenses among flying personnel

of the Royal Air Force during the second world war. A plea is made for increased care in the selection of persons to be fitted with contact lenses.

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THE NATURE OF THE MALIGNANT CHOROIDAL MELANOMATA*

BY

EUGENE WOLFF

LONDON

WRITING in 1904, Parsons upheld Ribbert's (1911) view that malignant pigmented choroidal growths were sarcomata, and is still of the same opinion. Dawson (1925) re-affirmed Unna's (1893) suggestion that these growths were epithelial in origin and therefore carcinomata, but the great majority of authors now hold the neurogenic theory, and believe that choroidal melanomata are derived from the cells of Schwann belonging to the ciliary nerves.

I would like at the outset to return to certain well-known basic

Dedicated to Professor J. Meller.

* Received for publication, March 9, 1949.

facts which latterly have not received the attention obviously due to them.

The cells of a sarcoma differ from those of a carcinoma in that they do not excite any local tissue reaction, whereas usually a carcinoma produces a well-marked stroma reaction, so that groups of epithelial cells become surrounded by fibrous tissue and hence assume an alveolar arrangement. That the choroid *can* produce such a reaction is shown by the fibrous tissue formed round secondary nodules from a scirrhus of the breast. The cells of a malignant melanoma behave like a sarcoma in that they produce no tissue reaction. In the (so-called) alveolar type of choroidal melanoma the boundaries of the alveoli are formed by blood-vessels or pigment, never by new-formed fibrous tissue.

The blood-vessels of a sarcoma are usually abundant, and present the characters of blood-vessels in the process of development, consisting of channels surrounded by a delicate endothelium, or possibly by actual tumour cells. In a carcinoma, on the other hand, the small blood-vessels, although they may be numerous, are confined to the tissues intervening between the cell-masses, and do not extend into the latter; they present the appearance of ordinary arterioles, venules and capillaries (Lawrence and Johnson, 1915). It will be seen that the blood-vessels of the malignant melanoma are identical with those of a sarcoma.

The cells of a sarcoma do not lie in actual apposition, but are separated from each other by varying amounts of ground substance. It is true that in a malignant melanoma of the choroid the cells are usually so closely packed that no intercellular ground substance is seen; but this may be present in varying amount, and can apparently always be demonstrated in teased preparations after fixation with chromic acid. Like a sarcoma, too, the spread of a malignant melanoma of the choroid is by blood-vessels, and only very rarely by lymphatics.

Ribbert (1911) showed that malignant melanomata could arise from branched chromatophores, and it has since been confirmed a great many times that a teased preparation of what on microscopic section appears to be a spindle-celled tumour of the choroid is in fact composed of chromatophores in all stages of development. The important fact brought out by Ribbert's work was that in secondary nodules found in the brain and liver there were cells identical with choroidal chromatophores. As further evidence of this I would emphasize that all the following types of pigmented and non-pigmented cells may be found in one and the same tumour: chromatophores with four, three, two, one or no processes. The last of these appear as large pigmented round cells (Figs. 1 and 2), and these pigmented round cells packed close together become

Figs. 1-5 are all from the same Tumour (Malignant Melanoma of Choroid)

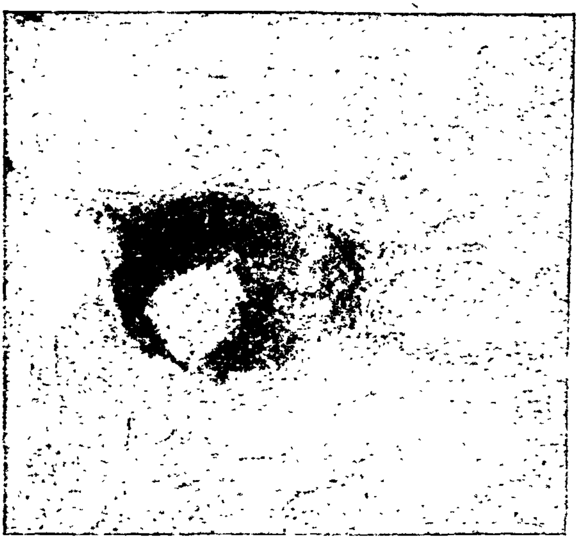

FIG. 1.

Typical chromatophore. The small round granules and the nucleus are visible

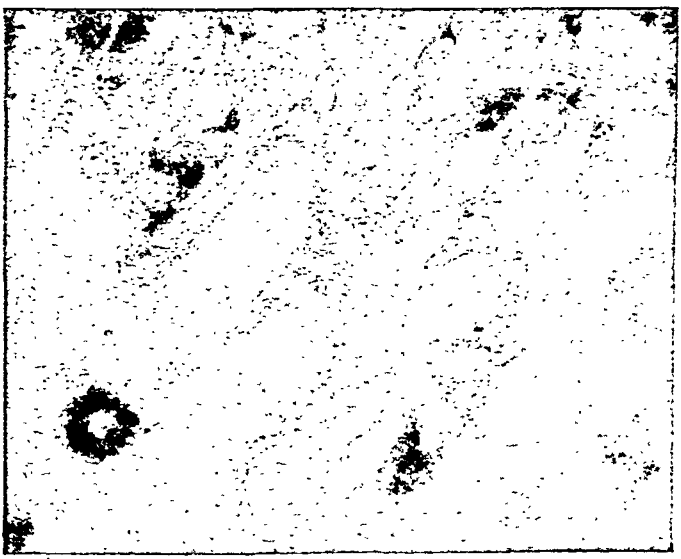

FIG 2.

Chromatophores with 4, 3, 2, 1 and no processes are seen.

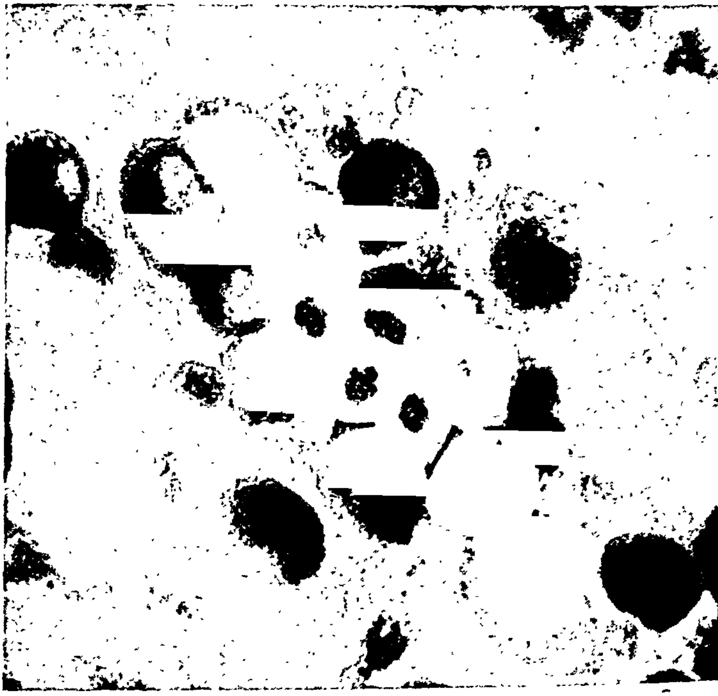

FIG. 3.

Large round and polyhedral chromatophores.

FIG. 4.

Slightly pigmented epithelioid cell.

polyhedral (Fig. 3). Finally there are pigmented spindle cells and pigmented small round cells. The nucleus is usually visible and is large, pale-staining, vesicular, with one or more well marked nucleoli. The following non-pigmented cells are found: large round cells like the pigmented ones but without pigment—these non-pigmented round cells when closely packed become polyhedral cells with large vesicular nuclei and abundant protoplasm (epithelioid cells) (Fig. 4), and finally typical spindle (Fig. 5) and round cells.

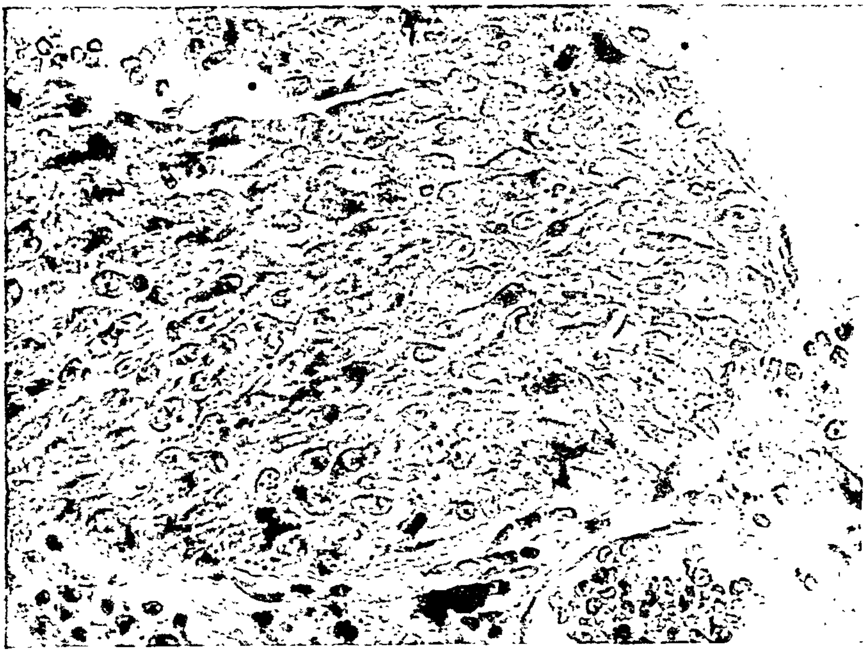

Fig. 5.

Portion of growth with typical spindle cells.

It will be noted that the general characteristics of the nuclei of all these cells are the same. Also the pigment in nearly all the pigmented tumour cells consists of small round granules of the same size, like those of the normal chromatophore. I would also stress the fact that there are intermediate forms of all the above-named cells, so that it might be quite impossible to say whether a given cell is spindle-shaped or epithelioid (Fig. 6). Thus a careful examination of a tumour containing all the above-named cells leaves little doubt that the chromatophore is the essential cell.

The fact that some malignant choroidal melanomata consist largely of epithelioid cells has been brought forward as evidence that the growth is or may be a carcinoma. The above explanation of the epithelioid appearance of the cells will, I think, rule out this suggestion.

The relation of the non-pigmented to the pigmented ones is, I suggest, that of the subconjunctival chromatophores in the fair and

FIG. 6.

Malignant Melanoma of Choroid. Epithelioid and spindle-cells in same tumour, with intermediate forms.

dark races of mankind. In the former they are usually non-pigmented, but the pigment can be demonstrated by the Dopa reaction or silver stains. There is thus no essential difference.

Finally Dawson's view that the pigment of the choroidal chromatophores comes from the retinal pigment epithelium cannot be upheld. (Collins, 1926; Mann, 1926; Wolff, 1948.) It will thus be seen, and this is a very important fact, that if there were no question of pigment the so-called spindle-celled choroidal growth

would in any other part of the body undoubtedly be diagnosed as a sarcoma and not a carcinoma.

Now we come to the claims of the neurogenic theory. The main reason why this has been brought forward is that it brings the choroidal growths into line with Masson's (1926) view with regard to melanomata of the skin. But there are serious objections to Masson's theory. In the first place definite *epithelial* downgrowths are well known to occur in simple naevi, and it has been shown repeatedly that these may develop into malignant pigmented growths. More fundamental still is the fact that the morphology, embryology and results of section of their nerve-supply appear to show that the tactile cells of the Merkel-Ranvier and Meissner's corpuscles are not derived from the cells of Schwann at all, but are developed locally in the epithelium (and are therefore ectodermal) and dermis (and are therefore mesodermal) respectively. (Wolff, 1948*b*.) This is not really surprising when we remember that in such sensory end-organs as a taste-bud the gustatory cells are epithelial.

Much has been made of the fact that there are nerves in the outer part of the choroid just where the choroidal growths usually start; but this is also where most pigmented cells are normally found. Theobald shows sections which she regards as proof that choroidal growths arise from the ciliary nerves, but all I can say from similar preparations of my own is that the cells of Schwann were continuous with the tumour cells, a relation produced simply by involvement of the nerve in the tumour, which is of course quite common. We must remember also that tumours of cells of Schwann are usually simple, only very rarely becoming malignant; and, as Willis (1948) points out, they are never pigmented. It would therefore be extremely curious if, with so many nerves in the body, the uveal tract were the only place where tumours arising from the cells of Schwann belonging to nerve-trunks, should be not only malignant but pigmented as well.

Finally we come to the origin of the chromatophores. Most observers hold that these pigmented cells are mesodermal in origin. Latterly, however, the suggestion has been put forward that the pigment cells are derived from the neural crest and grow down with the nerves to the skin, etc. This suggestion is largely based on the experimental evidence that a transplanted neural crest will develop pigment. The fact is, however, one cannot be sure that in transplanting so small an area as the neural crest a few adherent mesodermal cells are not transplanted as well.

It is therefore concluded that, in the present state of our knowledge, we should regard the malignant choroidal melanoma as a sarcoma.

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STUDIES ON THE INTRA-OCULAR FLUIDS

Part 3.—The Penetration of Some Nitrogenous Substances into the Intra-ocular Fluids.*

BY

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and

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EXPERIMENTS on the rate of penetration of sugars (Duke-Elder and Davson, 1949) and salts (Duke-Elder, Davson and Maurice, 1949) from the blood into the intra-ocular fluids reported earlier in this series have revealed a selectivity in the barrier separating these fluids, inconsistent with the conception of penetration through a simple pore-structure such as would be provided by the intercellular spaces of an endothelial or epithelial membrane. We were forced to conclude, on the basis of these studies, that the penetration of many substances into the intra-ocular fluids represented a trans-cellular process since it is only in the membranes of cells that we can expect to find a selectivity of the type described (Davson and Danielli, 1942). Experiments on the penetration of some amino-compounds—creatinine, urea, glycine, and alanine—to be described here, support this view. The above-named compounds have the following molecular weights :—

Creatinine, 113	Glycine, 75
Urea, 60	Alanine, 89.

Dedicated to Professor J. Meller.

* These experiments were carried out by E. J. Ross working in this laboratory: see *Brit. J. Ophthal.*, 33, p. 310. Received for publication, March 12, 1949.

METHODS

The general methods of raising the blood concentration of the substance studied have been described earlier (Duke-Elder and Davson, 1949): in all cases the renal arteries were tied to prevent too rapid an elimination of the injected material.

Chemical. Urea was determined by the method of Conway (1947); amino-acids by the Danielson (1933) modification of the Folin-Wu (1919) method on tungstic acid filtrates, and creatinine by the Folin (1905) method on similar filtrates.

RESULTS

The results are shown in Table I, the parameters K'_A and K'_V indicating the relative rates of penetration into the aqueous humour and vitreous body respectively.

TABLE I

Substance	No. of Expts	100 K'_A	100 K'_V	K'_A/K'_V
Creatinine	8	12.9 ± 1.2	0.79 ± 0.13	16
Urea	12	14 0 ± 0.9	7.0 ± 1.2	2
Glycine	3	15.5 ± 2.3	0.6 ± 0 5	26
Alanine	5	13.3 ± 2.4	1.0 ± 0 5	13

It will be noted that the rates of penetration of these substances into the aqueous humour are not significantly different, being in the region of 13 to 15 : the rate of penetration into the vitreous body, however, is very much slower, and among these substances urea stands out from the other compounds studied in entering very much more quickly, showing a value for K'_V of 7 as against values in the region of unity.

DISCUSSION

It may be noted that the nitrogenous substances considered here pass from the blood into the aqueous humour slowly and with apparent difficulty. It is interesting and important that they do so at considerably lower rates than the monosaccharides (K'_A 32·5) (Duke-Elder and Davson, 1949) and sodium (K'_A 37·6) (Duke-Elder, Davson and Maurice, 1949). Urea, for example, with a molecular weight of only 60, penetrates at about half the rate of glucose which has a molecular weight of 180. It is obvious that on the basis of a process of transfusion through a simple pore-structure (as occurs in most tissues of the body) the rate of penetration of urea should be considerably faster. The slow rates of penetration of creatinine and the amino-acids into the vitreous

body is interesting and agrees with the general concept developed earlier (Davson and Duke-Elder, 1948) that the barrier separating the blood from the vitreous body is more selective than that separating it from the aqueous humour. The fact that urea, on the other hand, penetrates so readily into the vitreous is interesting: it may be suggested (at this stage purely as a conjecture) that it may, like the sugars, enter by way of the retinal and uveal capillaries, while the other substances may be restricted to the latter.

SUMMARY

The rate of penetration of certain nitrogenous substances (creatinine, urea, glycine and alanine) from the blood into the intra-ocular fluid has been studied. The rate at which they cross the blood-eye barrier is much slower than can be accounted for by a process of simple transudation or dialysis through inter-cellular spaces and suggests a transference through cell bodies.

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INTERSTITIAL KERATITIS OCCURRING IN A CASE OF REITER'S DISEASE

BY

E. E. CASS

GIBRALTAR

A NUMBER of cases have already been described in the literature. All of them have the variants of diarrhoea, urethritis, polyarthritis, conjunctivitis and iritis, etc., but as far as can be discovered no case has previously been described with interstitial keratitis.

A case of Reiter's disease was admitted to the Military Hospital, Gibraltar, in 1946. He was, as is usual, a young healthy male of 24 years of age. He had had no venereal contact for 3 months and no history of previous venereal disease. His first symptom was dysuria for 12 hours and then a muco-purulent discharge from the urethra, and within 24 hours of its appearance he was in Hospital. Smears revealed pus and epithelial cells, but no organisms, and no organisms appeared on culture. There was a slight temperature only. The complement fixation test for G.C. and the Kahn and Wasserman were negative.

Treatment with sulpha-thiazole gave no results, and eleven days after commencement of treatment he developed a conjunctivitis with no discoverable organisms in the discharge, and simultaneously his left knee joint became painful. The leucocyte count was 10,500 per cu. mm.

	Per cent.
Neutrophile polymorphs	79·5
Eosinophiles	Nil
Basophiles	Nil
Lymphocytes	14
Monocytes	6·5

The conjunctivitis gradually recovered within a few days and the pus began to clear from the urethral discharge, but the knee became more swollen and slightly painful. The orthopaedic surgeon reported much effusion and some local heat, with restriction of movements. The synovial membrane was not swollen. Nothing abnormal was seen on X-ray.

With rest in bed the joint became less swollen, but about a fortnight later the patient complained of gradually failing vision in the right eye, without any pain, and the eye was flushed.

When he was referred to the eye clinic a "ground glass cornea" could be observed as the patient walked across the room, but he had no pain nor photophobia, although there was a ciliary and conjunctival flush.

On examination the right vision=6/18 N.I., left vision=6/6. Interstitial and deep keratitis were present in the right eye. The ocular tension was normal, but the A.C. was deep. The pupil was small and fixed, and the fundus of the eye could not be seen clearly.

The left eye was normal.

The Wasserman was repeated and was again negative. Routine treatment was given for the right eye, and a week later the left eye became flushed. The right pupil had dilated poorly with atropine, the cornea was clearer, and the iris could be seen, with enlargement of its vessels. On slit-lamp examination of the right eye, residual interstitial keratitis was seen. The endothelium was swollen, and showed a mass of white lines. The anterior surface of the lens capsule was covered with a brownish network, with brown spots.

The right eye cleared slightly in the course of the month, but iritis began in the left eye. In this eye the attack was severe, and within a week the tension was low, and the vision diminished to finger-counting.

All investigations as to cause were negative. Penicillin was given intramuscularly (1½ million units) with no effect.

This young man was finally invalided home with eye symptoms still persisting.

The theories and treatment of this disease have been discussed in many recent papers, and I am only publishing this case as it presents interstitial keratitis combined with keratitis profunda and iritis.

The most significant feature of this case was the development of new signs in different parts of the body, and the recovery of the old. Particularly severe and persistent were the eye signs. Secondly the absence of pain was notable.

My thanks are due to Colonel Townsend, D.D.M.S., and Lt.-Col. Creagh, R.A.M.C., for their kind permission to publish this case.

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OBITUARY

GEORGE MACKAY

It is with deep regret that we have to record the death of Dr. George Mackay, of Edinburgh, in his 87th year. Although his retiral from practice some years ago meant also his absence from most of our professional meetings, he has been held in affectionate remembrance by his few remaining contemporaries and by the senior members of a somewhat younger generation.

George Mackay was born in 1861 near Madras, where his father, also George Mackay, was serving as Deputy Surgeon-General of the Indian Army. He had another link with the military profession through his grandfather, Col. George Mackay, of Brighouse, Sutherlandshire, who, at the end of the 18th century, raised and commanded the Reay Fencibles.

When four years of age he came home to Scotland, where he received his education in Inverness and subsequently at Edinburgh University, where he graduated in Medicine in 1883. After a period of post-graduate study on the continent, he settled in Edinburgh, where he earned a high reputation as a clinician and as a surgeon. For 24 years Mackay served the Department of Ophthalmology of the University and Royal Infirmary of Edinburgh, and was an enthusiastic member of the Ophthalmological Society of the United Kingdom, the Scottish Ophthalmological Club and the French Ophthalmological Society.

His professional life was a busy one, but he had many outside interests. As a student he found time for athletics and gymnastics, and in later life applied himself to golf and fishing. He was also a member of the Royal Company of Archers, the King's Bodyguard for Scotland. Gaelic literature, archaeology, anthropology and geology claimed a good deal of his active interest. He was also a foundation member and subsequently president of the Clan Mackay Society. He maintained to the last his links with continental friends through his membership of the French Ophthalmological and Franco-Scottish Societies.

George Mackay's friendships were based on an essentially sincere and tolerant nature, and all alike were impressed by his unaffected natural courtesy. He has left none but the happiest memories with those who had the good fortune to count him among their friends.

A.J.B.

D. M. MACKAY

DUNCAN MATHESON MACKAY was a versatile ophthalmologist, who found time to pursue antiquarian and historical interests, and to play an active part in the work of the Presbyterian Church, as well as leading a busy professional life. He was for many years a familiar figure in the North of England Ophthalmological Society, of which he was chosen President in 1933. Among the other institutions which benefited from his activities are the British Medical Association, the Hull Medical Society, and Hull University College. His retirement from the staff of the Hull Royal Infirmary in 1929 was not destined to be permanent, because he returned in 1939 to fill a gap. Throughout the devastation of bombing raids, which incidentally destroyed his own home and equipment, Dr. Mackay continued to serve the Infirmary. In 1945 he returned to Scotland, and went on practising in Glasgow until a short time ago. He was in his 80th year when he died on April 12 at Campbeltown, Argyllshire. Among the ranks of ophthalmologists are many who will gratefully recall Dr. D. M. Mackay's courteous encouragement, and will remember with admiration his record of loyal service.

BOOK NOTICE

Text-Book of Ophthalmology. By SIR W. STEWART DUKE-ELDER. Vol. IV. Pp. xxiv and 1157, 1081 illustrations, including 71 in colour. Henry Kimpton, (London). 1949. Price, £3 10 0.

It is more than twenty years since Parsons* wrote: "We can imagine a demon at each level who would know everything about every level below his own, and nothing about higher levels except what was dependent directly upon the known processes of his own and lower levels. Above the top we can imagine a super-demon who would know everything." *Almost* we could be persuaded, as we glide through the pages of this magnificent volume, that here at last we are face to face with the super-demon. The author himself is a modest man, who would be the first to proclaim the limitations of his knowledge. Nevertheless the illusion of a super-demon persists. There is something uncanny in the notion of a mortal endowed with the swiftness and concentration of effort that must have gone to the making of so great a work. The achievement would be astonishing if it were the culmination of many years' whole-time effort, but the fact that this text-book has been written

*Parsons, J. H. Introduction to the Theory of Perception Cambridge 1927.

in the intervals of a busy professional life, interrupted by research, by long journeys and by innumerable other activities, seems nothing short of a miracle.

Originally Volume IV was expected to include diseases of the ocular adnexa, operative surgery and various other subjects which must now be relegated to Volumes V and VI. Neuro-ophthalmology, *Abnormalities of the Pupil, Disorders of Motility*, and Anomalies of Refraction including Aniseikonia, are considered in Volume IV, and within this range of subjects the reader will find everything set out in beautiful proportion. The first chapter (No. XLII) appropriately begins with a tribute to Harvey Cushing, and the book proceeds with the orderly tramp of a Roman legion to its splendid conclusion. Many of the illustrations are original, but the literature of the world has been ransacked for additional pictures, and the firm of Henry Kimpton deserves congratulations for so skilfully arranging this mass of material.

The problems of refraction, neuro-ophthalmology and disorders of motility are so much interlocked that they are especially difficult to handle, but Sir Stewart manoeuvres this unruly team with the ease of a ring-master controlling a troop of horses. In Somerset Maugham's *Cakes and Ale* Mr. Ashenden offers an amusing recipe for the author seeking fame: "His production must be such that if he cannot captivate a reader by his charm he can stun him by his weight." Certainly the *weight* of Sir Stewart's output would be staggering, even if it had all been written in a style like the trickle of sawdust; but his work is as charming as it is bulky. Let the reader beware, if he intends to devote a few spare minutes to looking up something in this book. His attention will be subtly beguiled, he will lose himself and read on with growing enchantment.

Volume IV of Sir Stewart's monumental text-book fully maintains the high standard of the three earlier volumes, and compels us to await Volumes V and VI with eager anticipation. Here is a great, wise, readable and beautifully produced book, which places every serious reader of ophthalmology deeply in the author's debt. In the felicitous phrasing of the Psalmist, "his line is gone out through all the earth, and his words to the end of the world."

FRENCH OPHTHALMOLOGICAL SOCIETY, 1949

The Annual Congress of the Société française d'Ophtalmologie was held in Paris at the Marcelin-Berthelot Centre from May 22 to 26. Now that the International Congress of 1950 is almost upon us, it was particularly fitting that a number of British ophthalmologists availed themselves of the opportunity to hear the leaders of French ophthalmology expounding their work. Also gathered together at these meetings were many distinguished ophthalmologists from other European countries, from Asia and Africa, from the United States and South America.

One whole morning session was devoted to discussion of the Report on Hypertensive Uveitis. It will be remembered that the Société française d'Ophtalmologie is accustomed to choose in advance one special subject for the main discussion, and that one or more ophthalmologists are entrusted with the preparation of a written report on this subject. The resulting work is published shortly before the Congress, so that members can become familiar with it before the discussion. M. Marcel Kalt, the principal author of this year's report, was warmly congratulated on his excellent work, which he lucidly introduced at the session of May 24th. Many other valuable contributions followed M. Kalt's opening paper. Papers covering a wide range of subjects were read at the other sessions, and it was delightful to hear so many of the voices with which we have already become acquainted during the last few years at meetings of the Ophthalmological Society of the United Kingdom and of the Section of Ophthalmology of the Royal Society of Medicine, and also at the Royal College of Surgeons. Instances which leap to mind in this connection are Professor A. Franceschetti, Drs. H. Arruga and J.-I. Barraquer, Professor G.-P. Sourdille and Dr. L. Paufique. Papers in the French language were also delivered by Mr. Frank W. Law and Mr. E. Wolff.

Two afternoons were devoted to clinical and operative demonstrations at the hospitals of Paris and its suburbs. Mr. T. Keith Lyle contributed to this part of the programme a talk on the orthoptic treatment of latent and manifest squint. A number of excellent films were also shown. Several of the visitors from Great Britain were conducted round the Hôpital St. Joseph by M. P. Mérigot de Treigny, who has proved himself a good friend to British ophthalmologists, unofficially as well as in his official capacity of Secretary-General to the Société française d'Ophtalmologie.

M. Edouard Hartmann has now succeeded M. Mérigot de Treigny as Secretary-General, and he certainly deserves the sincere gratitude of British visitors to the French Congress, on account of all that he did to make them feel welcome. Nor must it be forgotten how

largely the success of this gathering owed to the generous entertainment of the ladies. Thus Madame G. Rennard and her eminent husband kindly invited us to a party at their country house near Malmaison after the official expedition to Napoleon's villa. Madame P. Mérigot de Treigny, Madame E. Hartmann and Madame S. Vallon also offered delightful hospitality. Others too numerous to mention played a part in making us welcome and putting us at ease.

Sir Stewart Duke-Elder presided at the Annual Dinner on May 24, and made his after-dinner speech in fluent French. The subsequent speakers were M. M. Appelmans (Louvain), M. M. Alvaro (Sao Paulo), Professor B. Streiff (Lausanne) and Professor V. Rossi (Pisa). The following British ophthalmologists attended the Congress: Mr. G. T. W. Cashell (Reading), Miss E. E. Cass (Gibraltar), Mr. J. H. Doggart (London), Mr. E. A. C. Drécourt (Jersey), Sir Stewart and Lady Duke-Elder (London), Mr. A. C. Houlton (Oxford), Mr. E. F. King (London), Mr. Frank W. Law (London), Mr. J. P. Lloyd (Oxford), Mr. T. Keith Lyle (London), Mr. A. F. MacCallan (London), Mr. J. Minton (London), Mr. E. S. Philps (London), Mr. F. A. Williamson-Noble (London), Mr. E. Wolff (London), and Mr. E. Zorab (Southampton).

NOTES

Honour

AMONG the recipients of Birthday Honours was Mr. T. Keith Lyle, who was awarded the C.B.E. for his services as Consultant in Ophthalmology to the Royal Air Force. We offer congratulations to him on this well-deserved recognition,

* * * *

Alexander Piggott Wernher Memorial Trust Fund

IN accordance with a scheme approved by the Trustees, an allocation of £4,000 per annum has been made for the award of travelling fellowships or grants in furtherance of the objects of the Fund, which are defined as being for "the prevention and cure of blindness and deafness in the United Kingdom and British Empire, and in particular research in connection therewith by financing medical men and students within the Empire to study methods and practices in all countries of the world." These awards will be made primarily for research in ophthalmology and otology, for periods of up to a year, but grants may also be given for short-term visits abroad to study new methods of investigation and treatment in these fields.

These funds will be administered by the Medical Research Council, and applications should accordingly be addressed to the Secretary, at 38 Old Queen Street, Westminster, London, S.W.1.

THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

AUGUST, 1949

COMMUNICATIONS

PSYCHOSOMATIC PHENOMENA IN OPHTHALMOLOGY*

BY

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I WISH to express my thanks to the Royal College of Surgeons for the honour they have done me in asking me to deliver this lecture.

Medicine owes a considerable debt of gratitude to the pathologists who, during the last hundred years, have so materially contributed to our understanding of the various diseases, but sometimes one wonders whether we did not pay a price for this. Several generations of physicians have been trained to look for structural changes every time a patient comes with abnormal symptoms. If no physical signs can be found, then the complaint is considered illegitimate, neurotic or psychogenetic, and the patient is taken none too seriously; but, since the complaint

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is real to the patient, and his symptoms distressing, he will often drift towards those who are more apt to listen to him. In some fortunate cases he consults a competent psychiatrist, but more often the several varieties of charlatans attract him.

When I began my medical studies shortly before the first World War, such an attitude was usual, at least in Paris. On the one hand were the organic diseases due to structural changes, and this constituted the realm of real medicine. In another group were the purely functional symptoms due to a perturbation in the physiology of some organs, and without being actually denied, such symptoms were considered with suspicion and treated lightly. In a third group were the mental diseases, the psychoses, a category quite apart, belonging to the psychiatrists.

Such a rigid classification was, of course, untenable, and many of the better physicians realized this. A change in outlook was bound to occur. It was at first easily accepted that organic diseases could produce functional or even mental symptoms. For instance, an organic disease such as a goitre could alter the normal functioning of the thyroid, with resulting tachycardia and other disturbances. One more step, and this functional disturbance would bring about emotional and personality changes, verging sometimes on the psychotic, in the patient with thyrotoxicosis. Organic diseases of the stomach would alter the normal production of gastric juices ; cellular diseases in the kidneys or sclerosis of the blood vessels were the cause of hyperpiesis; and it was accepted that the structural changes in a brain tumour or in general paresis could result in severe mental disorders. There are many other such examples.

We must note that all these reactions from one category to the other go in the same direction—from the organic to the functional and possibly the mental, downstream from the legitimate to the lesser. For a long time established medicine would go no further, but in due course the prejudices broke down, and it had to be admitted that some disturbances travelled upstream. Thus it was realized that a lasting functional disturbance could result in a true organic one. For a long time the physiological imbalance was pure, uncomplicated and therefore reversible. If, however, it persisted long enough, structural changes would appear. The pathogeny of high blood-pressure and of gastric ulcer came to be interpreted in that light, and this " *upstream* " relationship between the functional and the organic is now generally accepted.

The next step was a more difficult one to take, and it is precisely the one which led to the psychosomatic approach to medicine, which became possible when the psychogenetic origin of organic lesions was accepted. At first emotional or psycho-

logical disturbances were considered capable of leading only to functional imbalance. Of this there are many examples in general medicine as in our own field of ophthalmology. Consider the numerous papers on ocular psychoneuroses causing photophobia, blepharospasm, convergence spasm, etc. The psychiatrists pointed out that, when patients were moved by various emotions, such as fear, anger, hate, sexual urge, these would normally influence the blood pressure, the endocrine secretions, the muscular tone, etc., but that, if the normal outlet was not offered, if all this could not culminate in the usual corresponding action and was repressed, then secondary and compensating reactions would appear, affecting the ductless glands, the vasomotor control system and several others, so as to produce corresponding functional disturbances. The last and most difficult step in this upstream sequence was to admit that purely psychological, emotional and mental disturbances could be the cause of organic diseases, but by now people were ready to accept that, if it lasted, the functional stage could lead to structural, irreversible and permanent damage. The pendulum had now swung all the way back, and so we come to psychosomatic medicine.

The study and practice of ophthalmology is unfortunately a bad training-ground for the understanding of such phenomena. More than others, we are accustomed to look for structural changes, since the transparency of the eye and the magnifying power of our optical instruments allow us usually to see them in the living patient who comes to us with his complaint, instead of having to wait for the *post mortem*, as the internist so often must. This is very unfortunate, since ophthalmologists should be highly interested in the psychosomatic approach to diseases, for two special reasons. In the first place, psychosomatic symptoms are very often mediated through the vegetative nervous system, and we know how important is its rôle in the eye. Secondly, the psychiatrists, and especially the psycho-analysts, teach us that the eye has a high symbolic value and will often be the site of conversion symptoms.

This leads me to discuss, at least in an elementary fashion, the pathogeny of psychosomatic symptoms and diseases. Every physician knows that a sudden emotion can cause functional symptoms, such as a sharp rise in the systemic blood-pressure. We ophthalmologists have often seen one of the most perfect examples of psychosomatic disease: a woman receives a wire bringing bad news, or is afflicted by the death of someone dear to her, and an acute attack of glaucoma sets in: the intra-ocular pressure shoots right up to 100 mm. Hg or more. This is the

functional stage, and if it does not last too long, it is reversible: with large doses of phenobarbital, repeated pilocarpine and eserine, a retrobulbar injection of novocaine and alcohol, all may return to normal. If, however, the high pressure lasts, the functional disturbances become irreversible and, should surgery be delayed, structural changes familiar to all of us will ensue. In a similar fashion, under the influence of various emotional disturbances, such as fear, anxiety, worry or a sentimental crisis, we may have patients come to us with other symptoms (*e.g.*, vascular spasms, ciliary spasms, etc.), and we feel that these functional disturbances are caused by an imbalance of the vegetative nervous system, *i.e.*, vegetative neurosis (Harrington).

Nevertheless, it is not enough to consider only the disturbing news, the emotional upset which was at the origin of the trouble, because only a few people will respond in that way to causes which, in most others, will evoke more sober manifestations. We must ask ourselves, then, where the difference lies. There is no doubt that a certain lability of the vegetative nervous system may be the explanation, and endocrine disturbances are often to blame, but let us not overlook the psychological background of such patients, and their personality pattern. To put it plainly, not everybody is apt to have an acute glaucoma or a spasm of the retinal blood-vessels. We can recognise what type of patient has acute glaucoma, for instance, and we are familiar with their emotional tenseness, their anxiety bordering on panic.

I have started with a striking example, but we should not ignore other and less dramatic forms of psychosomatic phenomena. Sometimes the emotion is not a sudden one, but consists in an almost permanent emotional tension. "Stress and strain" as a cause of hyperpiesis is generally accepted, but we must know that there is the equivalent in ophthalmology. It is difficult to over-emphasize the importance of this chronic psychological tension in chronic glaucoma, for instance, or in some vascular diseases of the retina, such as central angiospastic retinopathy. Here again one should not overlook the psychological and personality background which is the deep underlying cause, explaining why some people, but not everyone, will break down under the strain. The emotion is not the whole story. How the patient can take it constitutes another vital factor.

I shall now come to phenomena which are less familiar to most ophthalmologists. For these you may not so easily accept, at first, the explanation given by the psychosomatic approach. I am referring to conversion symptoms. It is difficult to deal with this without using to some extent the vocabulary of the psychoanalysts, but a few examples will make their meaning clearer.

In some patients there is a deep unsolved emotional conflict which permanently causes imbalance and psychological tension. The conflict may be a family problem or domestic situation familiar to the patient. We shall probably elicit such things from him if we question with patience and sympathy, but obstacles arise in some cases. Often—more often, the psycho-analysts will say—the emotional trauma dates back to childhood and has been repressed, barred from the clear consciousness of the patient. It will rankle in the subconscious, and tint the whole personality. Now and then it will come to the surface under the form of a pathological symptom which is an outlet for the hidden, unknown emotional tension. It will emerge in unexpected fashion, so that we will often overlook the underlying cause.

It is not often that the ophthalmologist can dig up this ancient cause, and more often psycho-analysts will publish such case-histories. Here is one which I owe to Dr. Leuba, a distinguished Paris psychiatrist :—

A girl aged 12 years, very grown-up for her age, and looking 16 years, was brought to him for instability, difficulty of adjustment to her school environment, and an obstinate laziness in spite of a brilliant mind. She would wet her bed at night every time she had been thwarted the day before, and at times there was a marked convergent squint. In many ways she showed her dislike of the female sex, and her refusal to belong to it. As she closed up under questioning, Dr Leuba resorted to having her draw freely. She made a likeness of him, then pierced both eyes with a pin, and at the same time her squint increased considerably. At another sitting she actually hit Dr. Leuba with the end of a wire, causing a painful superficial corneal abrasion. The next time the child came, somewhat subdued, she drew a body with two heads, a symbol of sexual intercourse according to Dr. Leuba, who tried to find out where and when the child could have seen this. The nurse, when questioned, explained that she herself had been seen by the child while having intercourse with the chauffeur. The child was about two years old at the time, and she had been standing up in her bed looking intently at the couple. Dr. Leuba was then able to help her to overcome the consequences of this repressed psychic trauma, and all her symptoms disappeared—the squint, the bed-wetting and the instability.

Weiss and English have pointed out that, since it is through the eye that we have very often, in childhood, seen things we were not expected to see, our repressed feeling of guilt will usually affect it more than any other organ : "*Persons so disposed* who have seen something which they consider improper, may react with squinting, blepharospasm, watering of the eye or hysterical blindness."*

A feeling of guilt will sometimes provoke ocular symptoms. My friend Dr. Reboul, of Toulon, told me about a patient of his suffering from mild chronic blepharitis. His condition became suddenly worse every time he had extra-marital intercourse,

* One should note the importance of the words "Persons so disposed." The same event will have very different consequences according to the individual personality pattern and psychological background.

whereas marital intercourse had no such untoward consequence. A patient of mine, with chronic glaucoma, had already almost lost the vision of one eye. A highly-strung, busy and intelligent man in his middle forties, he comes in regularly for a tension check, and in the meantime he is on a constant look-out for coloured rings as a warning of hypertension. In particular he looks at the flame of his lighter every time he takes a new cigarette. Usually faithful to his wife, he has in the past year had a few slips, and on each occasion he noticed coloured rings, but never when his wife was the partner of his intercourse. With regard to this feeling of guilt as a cause of distressing symptoms, one must note that patients will naturally consider their ailments as a merited punishment. My friend Dr. Reboul told me the amusing story of a patient with toxic amblyopia. When he asked the victim whether he drank and smoked, the answer came: "No, but I must admit I gamble." Disease as a just retribution is a fairly widespread conception. In my experience the unnecessary use of dark glasses often signifies an unconscious feeling of guilt. The patient seems to hide behind them.

Family conflicts will often affect children, and we are all familiar with the frequency of parental strife in the homes of squinting children. Inman, Pugh and many others have stressed this. Some time ago a boy of 16 was brought to my office. Since the age of 10 years he had exhibited a constant blinking tic. There was no local cause, and, as usual in such cases, the child was nervous and highly strung. A careful history showed that this tic, together with enuresis, had appeared at the time of his parents' divorce. The enuresis lasted only a few months, but the tic persisted.

It is not often that we ophthalmologists see our patients often enough and get to know them sufficiently to discover what the psychiatrists call an "Oedipus complex," but I know of several cases where the cause of the ocular symptoms can be traced to a probable feeling of jealousy at the time of a child's marriage. Here are two such instances:—

I had seen at regular intervals a woman in her late forties with hyperopia and presbyopia. One year, at a few months' interval, I twice had to diminish the strength of her spheres. There were no lenticular changes, but her blood-sugar was high. This condition responded to a proper diet, and the refraction returned to its previous level. During the next two years such attacks of hyperglycaemia occurred several times without any change in her diet. I happened to know the family fairly well, and found out that the initial attack had occurred when she first learned that her eldest son considered becoming engaged. This she violently opposed, and for two years her son hesitated, sometimes giving up his plans, sometimes returning to the girl. The attacks of hyperglycaemia always coincided with the latter. Finally the son married, the mother became reconciled, and the blood-sugar returned to normal and remained so. There were no more of these transient changes in her refraction.

A man in his late forties enjoyed perfect health until a much loved daughter got engaged. Thereafter he suffered constantly from severe heartburn, and he developed a moderate bilateral ocular hypertension (35 to 40 mm. Hg.). This responded inadequately to miotics, and an operation was considered, but, soon after his daughter married, his symptoms disappeared, and the tension has remained normal during the next two years.

An inferiority complex, or—to be more exact—a feeling of being inferior to one's task, I have sometimes met as a cause for ocular symptoms.

Here is a short case-history of a girl aged 27 years who came to me for the surgical cure of a convergent squint of 10 to 15 degrees. This esotropia had appeared two-and-a-half years previously, and since that time the patient had suffered from constant diplopia which prevented her from reading. Her hyperopic refraction was well corrected. The esotropia would vary, and I regarded the trouble as a spasm of convergence. The girl was nervous, scrupulous and not very bright. She had worked for several years during the war in a quiet government office. In 1945 (she was then 24), the war being over, her department became very active, as it was concerned with rebuilding some of the 4,000 bridges which had been destroyed in France. The patient worked slowly, and was unable to keep up with the rest of the office. She would work late in the evening, but definitely felt that she was inferior to her task, and would never be able to cope with it. Then her diplopia first appeared. Initially it was only occasional, but it became permanent after the head of her office took a dislike to her and scolded her almost daily for her poor work. She gave up her appointment, but the squint and the diplopia persisted. She was refracted repeatedly during the next two years, and glasses were changed as often, but that did not avail. After 4 months of orthoptic treatment with the major amblyoscope, she was cured of her convergence spasm and made comfortable. I advised her not to return to her former office, but to choose an employment with fewer responsibilities and a more sympathetic environment. She was to report if any trouble occurred. I have only heard from her by letter, but for the last two years she has been getting on comfortably.

One often notes the cumulative action of several causes, some organic, some psychic.

A young man of 24 was referred to me, with a myopia of 3 dioptres, and a 20/20 vision in both eyes, for a convergent squint. This had first appeared at the age of 4 during an attack of infantile paralysis. Glasses were prescribed, and by the age of 7 the esotropia had completely disappeared. I have no data on his fusion at the time, but it must have become normal, since he was greatly distressed by diplopia when he started squinting again at the age of 20 years. He had, in reality, a marked but variable convergence spasm which at times was as high as 25 degrees. There was presumably, at first, an organic cause for this muscular trouble. Probably the cure was not complete, and the stereopsis poor, so that there remained a weak spot ready for future trouble. The history revealed that what started this new squint was a deep emotional upset when his brother-in-law died. He was fond of him and genuinely grieved, but also his own life was considerably changed. He had always loved music and was devoting himself to it. When his brother-in-law died, the patient's father made him leave his musical studies and come with him to the family factory. This was a great disappointment to the boy. Also he was brought back into direct contact and under the tyrannical authority of his domineering father. I do not know which was the worse for him. Later I got to know the family a little better, and it was a strange one. The father was loud-spoken and domineering. I found myself in conflict with him several times, and I understand that this was his usual attitude in the family. The mother was a gentle, meek, evidently downtrodden little woman. She never dared say a word when her husband was present, but would show she had an excellent mind as soon as he was away. The boy of 24, our patient, reflected his mother's attitude, being also in terror of this tyrant who headed the family.

I could report several such instances in which organic and psychic causes intermingled, or rather added up, and every one of you knows of similar cases. It is usually a mistake to ask: "Is the cause organic or is it functional?" Rather should we wonder: "How much of the one, how much of the other?" This leads me to make a distinction between ocular disturbances entirely due to a psychosomatic factor and those in which the latter only starts the trouble or makes it worse: the organic reason is at the bottom, the psychic one causes the onset or the setback. Psychiatrists will tend only to see the former type, but we ophthalmologists will deal more often with the latter.

It is essential to bear in mind the possibility of such a complex aetiology. Overlooking this may lead to serious mistakes. If, for instance, there is a history of emotional upset or some other psychological disturbance, we must not jump to conclusions and be satisfied with dismissing the case as psychosomatic. We must carefully ascertain the physical condition, for quite often some organic trouble will also be present. Conversely, if we find an organic condition, we must always ask ourselves if this is serious enough to explain all the symptoms. If not, we must try to find out whether some psychosomatic reaction does not also come into the picture. Such often obtains in minor refractive errors. A perfectly normal eye is rare. If we come across a 0·25 or a 0·50 error let us not consider this a satisfactory explanation for all kinds of functional disturbances. Especially if the patient is young, we must not be satisfied with merely prescribing these weak glasses, but rather must we try to find out whether something else, far more important, is the root of the trouble. We will sometimes discover surprising psychological disturbances in a few minutes' conversation.

In such cases where organic and psychic causes interact, there is another pitfall. We must be careful not to stress the slight organic abnormality too much, or we may get the patient worried about this. He may concentrate on it and get even worse. If, for instance, there is some minor refractive error, it may be better to ignore it, or else we must put it in its proper light and explain that, in normal times, such a slight error would be easily overcome by his muscles, that his temporary upset condition is the reason for giving him glasses, that these will help him, but that as soon as he is better he will be able to discard them, because there is nothing organically wrong.

I have throughout assumed that the psychic trouble could cause the organic one, and that the symptoms were an outlet for an emotional tension, but this is a moot point, and there may be a different interpretation. In some cases there may be an initial

organic disturbance which will cause psychic and somatic symptoms alike. The former are, however, apt to be more obvious, and may afford valuable information (Marty). In that light must we think of the hypothalamic area. It is well known how essential is this part of the brain to our emotional life (Cannon). Here will originate nervous stimuli highly important in the visual function, vaso-motor control, regulation of the intra-ocular pressure, control of pigment distribution, etc. At the same time, directly or indirectly, emotional stress can affect the adrenals, pituitary, gonads and thyroid, and all of these may in turn react on the eye, its tension, circulation or motility. By following this train of thought, Magitot was led to consider, not that emotional factors could cause glaucoma, but that there is originally a diencephalic disturbance which causes both the ocular hypertension and the highly emotional personality of the patient.

I have mentioned some of the psychic disturbances which may cause ocular symptoms, but I have overlooked many more. I have only dealt with what we ophthalmologists can observe or learn in the course of a short conversation with our patients, but it is only the psychiatrists who have the time and the training necessary to expose the underlying causes. It must be well understood an emotional factor initiating functional or somatic troubles is not the whole story. Most people will "take" the psychic trauma, and only a few will develop symptoms. An abnormal personality is necessary for this.

Here is a case-history which will show the psychological disturbance acting at two different levels: in the near past it starts the trouble, in the distant past it had created the abnormal personality which made effective the recent emotional upset. A movie actress in her middle thirties complained of bad vision in the distance, dizziness, headaches, general poor health and fatigue during the last few months. She had had the same glasses for over ten years (-0·25 sph., -0·75 cyl. 90) and believed that they were responsible for her trouble. I found the spheres too weak, and changed the 0·25 to a 0·50, making no alteration in the cylinders. The muscle-balance was normal. The patient came back a few weeks later, stating that she could see quite comfortably at the movies and theatre now, but that she was still unhappy driving her car: things seemed to move on either side of her when she looked straight ahead, and the road seemed either to rise in front of her or swerve to the side. The headache and dizziness persisted. A second check-up satisfied me that my first prescription was correct. The change of glasses being so slight, I was surprised that it had not been easily accepted by this relatively young woman. I therefore questioned her to find whether something had been upsetting her lately. She had been playing for the movies steadily for over 15 years, but during the last half-year she had been given no parts. She felt that she would never be given one again, that she was probably considered too old now, and less attractive, and she was worried about her financial future. It was only since she had started worrying that she had found her glasses unsatisfactory and that her other symptoms had developed. In fact there were more of these than she had previously mentioned: a constant pain in her stomach, an occasional diarrhoea, and now and then what seemed to be extrasystoles.

I felt that all this was disproportionate with her worry, especially since the latter was probably unjustified, so I tried to find out something of her psychological background, and learned a few interesting facts. When she played, either for

the movies or the legitimate stage, she would now and then "see" a word ahead of her, usually several lines away which she felt certain she would not be able to pronounce. When she came to it, all the muscles in her face and neck would tighten, and she was only able to get the word out moderately well by a tremendous effort of will-power. The words she felt she would not be able to pronounce were not always the same, nor did they begin with the same sound. A psychiatrist would certainly be interested in having a list of these words, for it might disclose the deep reason for this inhibition. She had always suffered from this, ever since her early childhood when she had to say her lessons in school.

It was becoming apparent that she was psychically far less normal than she appeared on the surface, that her neurotic background might account for her being severely upset by a minor and momentary worry, and that the cause of all this should be sought in her early years. So I questioned her further, and found that her parents divorced when she was three, that her mother re-married at once and left with her for a distant country, and that she never saw her father again. He had died since. Her stepfather she hated, for he had been unkind to her and had made her childhood miserable.

I made no further changes in the glasses, and I advised the patient to consult a psychiatrist.

We can see in this case that the psychological upset which starts the trouble is not everything. For it to be operative, as a rule the personality has to be affected by a deeper and more lasting imbalance.

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I have given a few examples of the several psychological causes which may produce visual symptoms. Another approach to the psychosomatic problems of ophthalmology is to consider what are the various ocular diseases or symptoms which may either be started or made worse by factors emerging from the psychical sphere. I shall now take this up rapidly and incompletely, since much has yet to be done in that field. In many cases we can only suspect the part played by psychological factors.

Glaucoma, whether acute or chronic, is often precipitated or caused by emotional upsets. Schoenberg, Culpin, Magitot, Harrington, Gros and many others have stressed this, and Hibbeler recently published an interesting study of the personality patterns of glaucomatous patients which she found to be definitely abnormal. In a less scientific way we are all familiar with the psychology of such patients: either highly strung, tense and psychically overtaxed, or over-sensitive and incapable of adjusting to an unpleasant environment, to domestic problems, to professional worries, and to more or less well-founded fears. One of my patients who suffered from glaucoma and various digestive ailments summed this up very well: "I am not a sick woman, I am an unhappy woman." War conditions have severely taxed some of these sensitive natures. Gros, who practices in Boulogne, a Channel port which was bombed over 500 times during the last war, published an interesting paper on this. The ocular hypertension in his patients was brought on by various emotional

shocks: broken engagement, husband taken prisoner, bombing, etc. Far more strange still are Inman's findings that an attack of glaucoma "may coincide with the anniversary of events once pregnant with emotion, but now apparently indifferent or even long since forgotten."

Vascular disturbances are sometimes caused by psychological factors mediated through the vegetative nervous system: spasms of the retinal arteries, possibly spasms of those bringing blood to the optic nerve, spasms of the cerebral arteries and hemianopia, with or without migraine, should be mentioned in this connection. Harrington published the interesting story of a U.S. Navy officer whose migraines were due to a feeling of being inferior to his new duty when he was put in command of a cruiser. He was only cured when he went back to a subordinate position. A vascular spasm was probably responsible when the Homeric warrior became suddenly blind at the sight of his threatening enemy. As Culpin pointed out, this is probably the first published observation of a psychosomatic disturbance.

When the spasm is prolonged it may lead to central angiospastic retinopathy. Zeligs observed several such cases in the U.S. Marines, and found that a state of acute anxiety due to the military situation was a common factor. Retinal haemorrhages or exudates will sometimes be observed to follow a rise in the systemic blood-pressure or an increase in the blood-sugar level. Both can, of course, be due to emotional factors.

The psychological study of squinting children is highly interesting, and much is still to be done in that field, but everyone agrees that psychological disturbances play an important rôle. Inman has stressed this, and Pugh considers that 20 per cent. of her cases are psychological squints (imitative squints, jealousy squints, fear or shock squints, difficult children, psychoneurotic parents, etc.). Muscular imbalance, heterophoria, vergence insufficiency, all these abnormal conditions may sometimes appear under the influence of psychological stress: worry, anxiety, fear, emotional upsets, domestic problems, etc. I have published several such histories, but psychological and organic factors usually both contribute in such cases. A mild anomaly, easily accepted in usual times, will suddenly cause serious distress when the patient is upset.

In a similar way do refractive errors, at times, bring on a discomfort out of all proportion with the physical condition. Many years ago Derby wisely advised against prescribing glasses to such patients complaining of asthenopia. A rather special case is the sudden appearance of a myopia due to a ciliary spasm. This is often psychosomatic in its appearance, but usually with an underlying abnormal somatic condition (Hyperopia).

Jelliffe ascribes myopia to a purely mental cause in some patients. He states that myopia appears at the time of puberty, and may sometimes be due to the patient's desire to exclude the outside world. He reports three cases of myopia: one with a narcissistic fixation, one with a perverse urge, and one with an Oedipus situation. These histories, however, are to my mind unconvincing. The ophthalmological side of the observations is non-existent; and, besides, either the myopia persisted and was a true myopia, only *coinciding* with the mental trouble (myopia is prevalent enough for this to be possible), or it disappeared and was really a ciliary spasm. I feel that such exaggerated claims for the mental causes of ocular diseases are apt to do harm.

Eye injuries are more or less likely to occur according to behaviour, and greater or lesser recklessness. Here again we can see how emotional stress may come into play. Dunbar has offered statistical evidence concerning the psychosomatic origin of many fractures, and this applies to other forms of trauma. I believe that some accidents are due to an imprudence which is almost desired by the patient's subconscious mind. They are the equivalent of an unadmitted suicide, and are often caused by emotional factors.

A blinking tic, with or without photophobia and lacrimation, will often be found to have an emotional background, and the attacks are usually precipitated by psychological factors. Blepharospasm is, of course, an organic state, but here again the spasms are often started by the trigger-action of an emotion. What causes Graves' disease, with its many ocular signs and symptoms, is still a moot point, but the importance of emotional stress is generally admitted, whatever may be the rôle ascribed to the hypothalamus.

In allergies, "an attack can be precipitated by an idea just as much as by an injection" was ably written by Gillespie, and his remark applies to ocular allergies as well as to others. We must not overlook the fact that besides the more usual allergic diseases we immediately think of, such as those of the conjunctiva, we must also consider the part played by allergy in the course, and in the relapses, of chronic infections.

Since psychosomatic disturbances are most usually mediated through the vegetative nervous system, and since nowhere is it more easy to recognize its tone than in the pupils, it is highly interesting to observe how these will respond readily to a psychological stimulus. This is well known to the layman; and how often does a novelist state that the pupils of his hero were dilated by fright? Any strong emotion will do this, but anxiety and fear are the most efficient ones (Bumke). A permanent dilatation, sometimes with a sluggish reflex to light, is found in many mental patients suffering from anxiety neurosis.

The pupils will also dilate suddenly under the influence of a painful stimulus (Budge), but this mydriasis is due less to the pain than to the mental state it has caused. It can also be produced by purely psychic factors, such as fear produced by suggestion, as is shown by Löwenstein's pupillographic studies. What he calls "the psychosensory restitution phenomenon" is most interesting in this respect: if a pupil is repeatedly stimulated by flashes of light, the photomotor reflex will gradually fatigue, and towards the 60th stimulation it will usually disappear, so that the pupil remains contracted. If a psychological stimulus is now applied—a suggestion of fear, for instance—the pupil will dilate, and the photomotor reflex is again prompt (see Fig. 1).

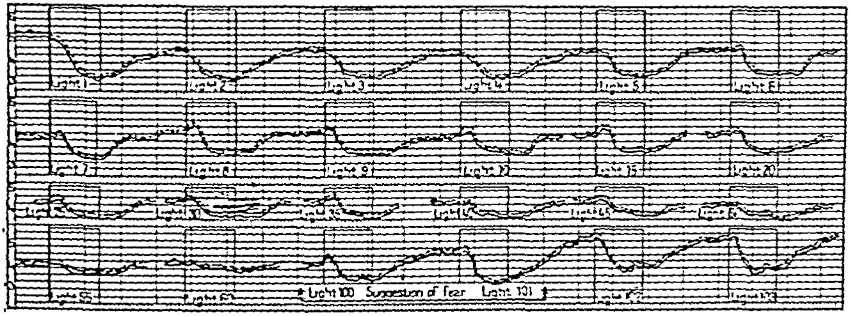

FIG. 1.

Pupillographic recording of a psychosensory restitution phenomenon The pupil was stimulated by light 109 times. The light reflex gradually fatigued and was absent after the 60th stimulation. Between the 99th and 100th stimulation the patient was subjected to a suggestion of fear. The pupil dilated at once, and reacted to light. Reproduced from Otto Lowenstein's "Der psychise Restitutionseffekt"

I would now like to mention the importance of psychosomatic phenomena in the course of chronic diseases. Diabetes, for instance, has, of course, an organic cause, but it is generally accepted that the onset can be caused by a moral shock, and also that, in the prolonged course of the disease, emotional factors can play an important part. I have just given an instance of such emotional changes of the blood-sugar level, and certainly there are many similar cases.

In the same way the part played by emotional upsets should be considered in the course of chronic infections, such as tuberculosis. Dunbar has stressed this, pointing out that these psychological factors may coincide with the onset of the disease or with relapses. I have noticed this several times in recurring uveitis. It is difficult to tell whether it is due to a sudden lowering of the patient's resistance to infection, or to a condition more favourable to allergic accidents. Both may have a close

relationship with the state of the vegetative nervous system, and we all feel that the latter can mediate psychosomatic disturbances.

It is above all in the central mechanism of vision that psychosomatic phenomena are evident. When the visual impulses have reached the calcarine area, they must be elaborated, integrated, and transformed into conscious perceptions. It is at this stage that psychological factors will be particularly cogent. A simple change in our degree of attention can considerably modify what reaches our full consciousness. At other times the disturbances can be more serious, and will produce visual suppression. Visual hysteria is naturally most prominent here, but other forms of neurosis—anxiety, for instance—can play a similar part. Hysteria is the most perfect type of a psychosomatic disease, but I cannot here dwell on its visual symptoms in detail.

The incidence and symptoms of war pyschoneurosis are of course very familiar to all of you here, since some of the best papers on it have been published in this country, mainly by medical men attached to the Armed Forces (Doggart, Campbell and Cross, Livingston and Bolton, Wittkower and his co-workers, Michaelson, Hurst, Mahoney and Linhart, Werner Bab, Cameron and Stephenson, Todd, Gillespie, Symonds, Curran and Mallinson, Johnson, Hall, Ramsay, Tostevin, Bland, etc.).

. . . . . .

Speaking for an hour on psychosomatic phenomena in ophthalmology will of course allow only a very sketchy outline. Every one of my paragraphs might be expanded and illustrated by detailed case-histories, but time will not permit. I shall leave this to others. May I only have made you conscious of the importance of such problems, not only from the theoretical but also from a practical point of view, because our therapeutic measures should be influenced by this outlook. We should probably prescribe less glasses and less medicines than we do, and talk with our patients a little more.

Of course we must realize our limitations. Often we can only suspect a psychological cause, and in serious cases this can only be ascertained by a psychiatrist who has the proper training and plenty of time. In many milder ones, however, we shall have to do the whole job ourselves: we must uncover the psychic disturbance, and we must help our patient. Of course we cannot turn into psychiatrists, but even elementary psychology, some understanding and simple human kindness will often prove useful.* More often we will need the co-operation of the psychiatrist, for the ocular symptom is only one of the ways in which

* The direct approach "What worries you?" is in most cases quite useless. The best way is to have the patient talk quite freely about himself, his life and his past. Much of interest may come to the surface during this conversation.

the patient will express his psychic conflict. If we relieve him of his present complaint another one will appear, usually in a different field from our own, for the trouble is with the total personality: there is a deep conflict, and the present symptom is only an attempt to escape from it.

Another reason for my wishing ophthalmologists to be aware of these problems is that it would be highly desirable for them to share in this exploration.* Up to now it has practically been abandoned to the psychiatrists, and especially the psycho-analysts. The consequence is that their case-histories are beautifully written up from the psychiatric point of view, but the ophthalmic part is sketchy, and usually unconvincing. We certainly will often need the help of the psychiatrists, but they need our trained services even more, if serious progress is to be made, and the whole thing not laughed to scorn.

Some will not readily accept this new approach to our familiar medical problems, since it changes our usual outlook, and has widespread implications. We must not ignore the fact that, if we grant to the mind such great power over the body, and, in particular, that of making it ill, we may have to admit that it has also the capacity to undo its own mischief and even to heal. Of course we can qualify this: we can say that it will only be possible in the early stages, before any irreversible structural changes have occurred, before any secondary effect is present; but, even with these limitations, it will be a hard one to swallow for many of us in the medical profession, because it will lead us to accept the idea that miracles did not necessarily stop some twenty centuries ago, but may possibly still occur. It will oblige us to reassess in a new light such miraculous cures as are sometimes claimed to-day.

But this should not be a serious argument against a psychosomatic approach to medicine, for it would be unscientific to accept or reject findings because of their consequences. One must assess the facts on their own merit. I myself am far from accepting a lot of published nonsense such as an Oedipus situation or a narcissistic fixation as the cause of myopia, but I am also far from considering any longer that mind and body are two things definitely apart, with no pathological link, as I was taught in my medical school days.

* The exploration is at present very incomplete, as is exemplified by the scanty space devoted to visual disturbances in the book on "Psychosomatic Medicine" by Weiss and English. In this 650-page volume only 2½ pages deal with visual symptoms. Considering the high symbolic value of the eye, and the considerable anxiety caused by any disease affecting it, I am convinced that psychosomatic phenomena must be very frequent in ophthalmology.

We must examine these problems with an open and a critical mind. I was Babinski's intern many years ago, and when a patient showed a surprising symptom, an unexpected one, he never ignored it as many would have done. He used to draw his chair nearer and say: "Il faut regarder cela de très près," which is approximately: "Let us look into this very carefully." This is the method that led him to present the medical profession with the plantar reflex and with so many other signs which have become indispensable to the neurologists. This is how we should act with anything new, and with psychosomatic medicine in particular: Let us look into this very carefully, critically of course, but with an open mind.

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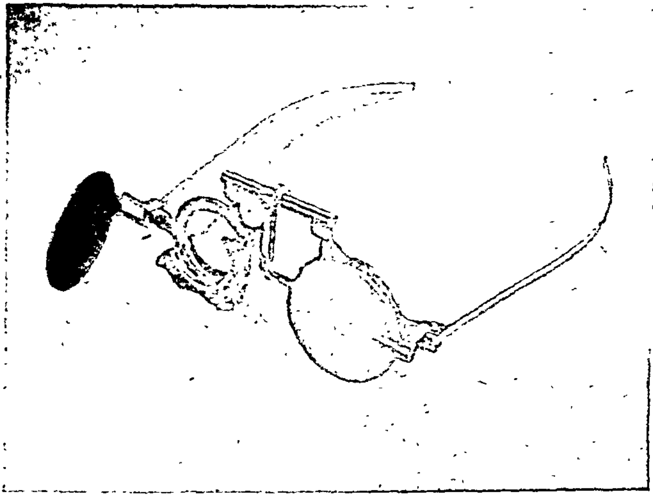

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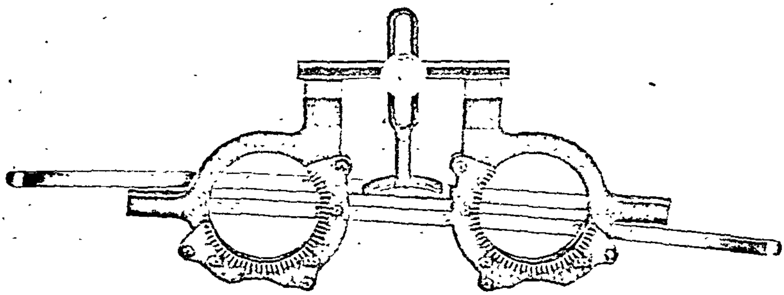

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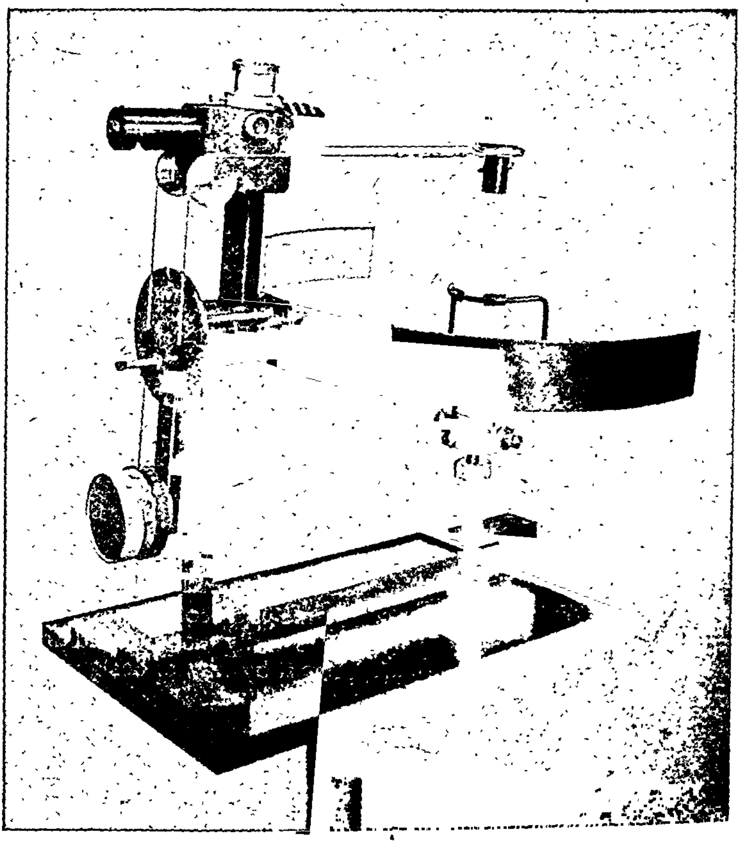

THE FINAL RESULTS OF SQUINT OPERATIONS, IN WHICH RESTORATION OF BINOCULAR SINGLE VISION WAS NOT EXPECTED*

BY

A. STANWORTH

MANCHESTER

THE purpose of this paper is to analyse the results of operations for cases of squint, in which restoration of binocular single vision was not expected, particularly with regard to the final state of binocular vision.

The clinical material consisted originally of 155 cases treated at the Manchester Royal Eye Hospital, in all of which it was considered that orthoptic treatment was unlikely to benefit the patients, or in which it had already been tried and abandoned. In the latter case the number of treatment sessions had rarely been more than ten, the usual practice in the Orthoptic Department being to give only short courses of treatment if obvious improvement failed to occur (Duthie, 1945). In the interval between the onset of the squint and the institution of orthoptic treatment, correction of the refractive error and any necessary occlusion treatment for amblyopia had been carried out. Of the 155 cases, 21 failed to report for follow-up examination; 26 were excluded because the pre-operative notes were either lost or were equivocal; 4 were excluded because they had received post-operative orthoptic training; and 4 were excluded because the period of time since operation (3 months) was too short to assess the final state of binocular vision. There remained 100 cases with satisfactory pre- and post-operative tests, and the analysis that follows concerns these cases.

DETAILED ANALYSIS

As a result of the synoptophore findings the cases were divided into four groups:—

1. Those in which binocular vision was absent. In these cases, with simple simultaneous perception (S.P.) slides, the two images could only be appreciated simultaneously when they were widely separated, and could not be seen to cross when they were taken past the macular regions, *i.e.*, there was dense central suppression.

2. Those in which simultaneous perception only was present, *i.e.*, in which the two images could be superimposed at the subjective angle.

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* Received for publication, August 14, 1948.

3. Those in which fusion with amplitude was present.
4. Those in which stereoscopic vision was present.

In order to assess the results more accurately, it has been considered that no appreciable improvement had occurred if the final post-operative reading was still "no binocular vision" or "simultaneous perception only" (*i.e.*, Groups 1 and 2), but that if the patient had developed fusion with ductions or stereoscopic vision, then obvious improvement had occurred. The few cases which showed some fusion before operation were excluded, and the 100 cases are divided into 60 with "no binocular vision" pre-operatively, and 40 with "simultaneous perception only."

Of the total of 100, 74 showed no appreciable improvement, 26 did improve, 20 developing stereoscopic vision.

Of the 60 with no binocular vision, 51 (85 per cent.) did not improve, 9 (15 per cent.) did improve, 7 (12 per cent.) developing stereoscopic vision.

Of the 40 with simultaneous perception, 23 (58 per cent.) did not improve, 17 (42 per cent.) did improve, 13 (32 per cent.) developing stereoscopic vision.

The difference in the percentage improving in the two groups is statistically significant, and the difference is made even more obvious when details of the nine cases improving from "no binocular vision" to fusion or stereoscopic vision are examined. Of these nine, four had only one pre-operative test, two had shown simultaneous perception several times, but not just prior to the operation, one had false associated fixation, one was a backward child and therefore unreliable, and one developed only weak fusion after operation. Therefore it is probably rare for a case to show the development of fusion or stereoscopic vision purely as a result of operation if binocular vision was originally absent. The prognosis is much better if simultaneous perception was present originally.

THE EFFECT OF PRE-OPERATIVE TRAINING ON THE RESULTS

Only 51 of the 100 patients had received pre-operative orthoptic training, though all had been tested on the synoptophore on one or more occasions. No comparison between the trained and the untrained group is worth while, since the former is obviously a highly selected group; but of the 51 patients who had received orthoptic training, all of whom had failed to respond to the training, 16 (32 per cent.) developed fusion or stereopsis after the operation. Twenty-nine of them had simultaneous perception before operation, and of these, 12 (41 per cent.) improved. Of the 22 with no binocular vision before operation, only 4 (18 per cent.) improved, and even this figure may be too high, as explained above. Nevertheless it

seems that after operation fusion or stereoscopic vision is developed in one third of the cases in which orthoptic training has produced no improvement.

RELATIONSHIP OF THE RESULTS TO THE TIME SINCE OPERATION

It is obviously of interest to determine, if possible, the period that elapses between the operation and the recovery of the binocular vision. None of the four patients re-examined within three months of operation had developed fusion or stereoscopic vision, and on the first analysis the results showed that those cases examined within twelve months of operation showed a significantly less percentage of improvement than those examined after more than twelve months. It could be shown, however, that this was due to the former group containing a larger number of cases with no binocular vision originally, and that if Groups 1 and 2 are considered separately, no such significant difference could be found. This suggests that in all probability a patient who is going to develop fusion or stereoscopic vision will do so within the first twelve months after operation, but a larger series, especially with repeated post-operative readings, would be needed to substantiate this.

THE EFFECT OF THE PRE-OPERATIVE VISUAL ACUITY

All except one of the twenty patients who developed stereoscopic vision had not more than two Snellen lines difference in the visual acuity of the two eyes; the one exception had an acuity of 6/36 in the worse eye, but at one time during treatment for the amblyopia the vision in this eye had been 6/12 partly. Of the six patients who developed fusion, only two had more than two Snellen lines difference in the vision of the two eyes and one of these developed only weak fusion.

In general, then, one can expect improvement only in cases with approximately equal vision; in this type of case, 44 per cent. of those starting with simultaneous perception grades 1 or 2, and 17 per cent. of those starting with "no binocular vision" improved in their binocular vision. It must again be emphasised that the second figure is probably too high.

THE EFFECT OF THE PRE-OPERATIVE ANGLE

The average angle of the squint in the cases with no binocular vision pre-operatively was 27 degrees in those which did not improve, and 29 in those which did. In those cases originally with simultaneous perception, the corresponding figure was 23 degrees in each group. It appears then that the size of the pre-operative

angle of deviation is of no significance as far as the post-operative state of binocular vision is concerned.

RELATIONSHIP OF THE RESULTS TO THE TYPE OF SQUINT

Since the patients whose tests are analysed were not seen personally by the writer before operation, and since their notes contained no definite statement by the surgeon in charge as to the type of squint present, it was felt that it would not be worth while to attempt to classify them at this stage. Nevertheless some indication of the types involved can be obtained by correlating the results with the age of the patient at the onset of the squint, the mode of onset, and the refractive error present. It is, of course, true that the parent's statements regarding the first two of these factors are not always reliable, but nevertheless the analysis is of some interest.

A definite statement of the age of onset was made in 72 cases; 19 of these developed fusion or stereoscopic vision, and in only two of these was the age of onset less than three years, one being at 2½ years of age and the other at six months. The latter was particularly interesting. He had never been treated by occlusion, but had developed equal visual acuity in each eye. There was practically no error of refraction present, and he was regarded as a "true alternator." He was operated upon at the age of 7 years and subsequently developed (from no binocular vision) stereoscopic vision. Nevertheless, an early onset of the squint appears to preclude improvement in the binocular vision except in rare cases.

Analysis of the effect of the mode of onset showed that it was in those cases ascribed by the parents to fevers, convulsions, or some form of shock that the greatest number with improved binocular vision occurred, 15 out of 36 (42 per cent.) gaining fusion or stereopsis. Those ascribed to a fall were an exception to this, only one out of ten improving, presumably because this group contains younger children. None of the fourteen cases ascribed to teething or heredity showed any improvement, and they too would obviously fall into a younger age group.

The effect of the refractive error was less definite. No patient with anisometropia of more than 1·50 D.S. developed fusion or stereopsis; of the others, a slightly greater percentage of those with a refractive error of more than 3 D, compared with those of under 3 D, improved in their binocular state, but the difference (37 per cent. compared with 28 per cent.) was not statistically significant.

Correlating all these results, it appears that under these conditions the state of binocular vision in a case of squint of the essential alternating type is unlikely to improve, whereas in cases of the unilateral type there is a much better chance.

RELATIONSHIP TO AGE AT TIME OF OPERATION

In general, the preferred policy has been for operation to be performed at about the age of seven years, after orthoptic treatment has been given a trial. Only one patient in this series was operated on before the age of six years, and that was at the age of $3\frac{1}{2}$ years. This child developed (from simultaneous perception) full stereoscopic vision. When the remaining cases were divided into five year groups according to their age at operation, no correlation could be found between this and the improvement in binocular vision, those operated on later than the optimum age showing equally good results. The greatest age at the time of operation after which any patient developed stereoscopic vision was nineteen years.

RELATIONSHIP TO THE POST-OPERATIVE ANGLE

Of the 40 patients who started with simultaneous perception, 31 had a post-operative angle of deviation of 0 — 5 degrees, and of these 16 (49 per cent.) developed fusion or stereoscopic vision. Of the other 9 with more than 5 degrees final angle, only one (11 per cent.) developed fusion, none gaining stereoscopic vision.

Of the 60 patients who started with no binocular vision 36 had a final angle of 0—5 degrees, and of these 8 (22 per cent.) developed fusion or stereoscopic vision. Of the remaining 24, only one (4 per cent.) did so, developing stereoscopic vision.

From this it appears that there is much more chance of developing good binocular vision if the eyes are put really straight. The two patients who obtained good binocular vision with angles of deviation of more than five degrees were both eight degrees divergent, but apparently this was not too great for them to overcome. It may be, however, that the small final angle may be the result rather than the cause of the development of good binocular vision; a decision between these two alternatives might be reached by a comparison of the immediate post-operative readings, taken two weeks or so after the operation, with the final readings. These figures are available in only eight of the cases in which improvement in the binocular state occurred; in these, the average angle immediately after the operation was 7 degrees, the average angle finally being three degrees, suggesting that the smallness of the final angle is the result rather than the cause of the development of good binocular vision.

DISCUSSION

These results show that straightening of the eyes results, in an appreciable number of cases, in the development of good binocular vision, even if pre-operative orthoptic training has been ineffective,

the type of case holding out most prospect of success being one of unilateral squint with an onset at not less than three years of age, in which the visual acuity has been made approximately equal in the two eyes, and in which simultaneous perception is present. Of this group, which includes 21 patients in the present series, 16 developed fusion or stereopsis after operation, *i.e.*, 76 per cent. Eleven of these patients had received unsuccessful pre-operative orthoptic training. Of the five who failed to improve, two had hyperphoria after the operation, one of 4 degrees and one of 14 degrees, which probably interfered with the development of binocular vision.

The question immediately arises as to whether or not the orthoptic training was sufficiently thorough. It is true that in many orthoptic departments much longer periods of training are given, but it is felt that the results rarely justify submitting the child to the disadvantages of such treatment (Duthie, 1945). In addition, all the cases in this series had shown no sign of progress under treatment, and it is unlikely that any but a very small number would have improved with a longer course.

There are few reported series of cases which can profitably be compared with the present one, since either the cases had not been selected in the same manner, or the operation had been followed by post-operative orthoptic treatment. That a large proportion of adult squints, which are usually considered to be unlikely to develop good binocular vision, can do so following operation has been shown by Shure (1944), 53 per cent. of whose cases aged 18 to 39 years obtained fusion or stereopsis. These patients, however, had post-operative orthoptic training, in view of which it would be interesting to try the effect of such training on a series such as the present one, and see if the final results were improved.

If, in this series in which are selected those cases unlikely to develop good binocular vision, 26 per cent. nevertheless do so after operation, it would be expected that a random series of squints treated, apart from the correction of the refractive error and amblyopia, by operation alone would show an ever higher percentage of good binocular vision. In the series reported by Berens, Elliot and Sobacke (1941), there were 144 cases of this type; 105 of these had no binocular vision or simultaneous perception before operation, and only ten of these (9 per cent.) improved their binocular state after operation. This figure is almost the same as the percentage improving due to orthoptic treatment without operation, given in their other series suggesting that had this type of case been removed from their first series, as is done in the present one, there would have been practically no patients who improved in their binocular state after operation. The difference between this and the present 26 per cent. improvement is striking and requires explanation.

The only other obvious difference between the two series is that only the present one had orthoptic treatment before operation, and it may be that this training, although not producing any obvious improvement in their binocular vision, did in some way alter the central nervous pathways so that subsequent improvement in binocular vision was made possible. This may be so, but a comparison of the results in the two other groups reported in the same paper, the difference between which is that only one received pre-operative orthoptic training, both receiving post-operative training, shows no significant difference between the results when analysed in the same manner as the present series, so that any favourable effect from pre-operative treatment such as is postulated above can probably just as easily be obtained from post-operative training.

In addition, such an effect from pre-operative orthoptic training presumably acts by the repeated stimuli through the central nervous system keeping the pathways open by some form of conditioned reflex mechanism, and such an effect might also be achieved by an earlier operation to put the eyes straight. Earlier operation might therefore be considered, not only for this type of cose, but also for those which do show obvious improvement with orthoptic treatment. In this way one could reduce or eliminate the waiting period which often occurs between the correction of the refractive error and and the amblyopia, and the institution of orthoptic treatment, a period which necessitates constant observation and treatment to prevent amblyopia, in which the loss of the stimulation of the central pathways makes subsequent re-education more difficult, and in which there is the possibility of the development of false associated fixation. Early operation is also of decided psychological benefit.

Pre-operative orthoptic training has, of course, its own advantages; a strongly developed fusion faculty before operation will help the eyes to become straight even if the operation corrects the squint only approximately; also one can assess the individual case much more accurately, and nursing at or about the age of seven years is much easier than in a younger child. Nevertheless the end results of such a series of cases operated on as soon as the squint occurs, provided glasses have failed to correct the squint and any amblyopia has been treated, would be of great interest. So far as I am aware, no such series with adequate follow-up examinations has been published, although earlier operation has, of course, been suggested and tried by several authors. Hepburn (1932), for example, thought that better results are obtained if the eyes are put straight before orthoptic treatment is instituted, saying that very little fusion training was then necessary, and stereoscopic vision may be obtained as early as a week after operation. Peter (1932, 1936), preferred operation as soon as possible after the age of three, both in unilateral

and true alternating squints, and Chavasse (1939) was also a strong advocate of early operation. In the case of the true alternating type of squint, which develops before the age of two years (Wheeler, 1942), and in which in all probablity fusion and stereoscopic vision have never been present, it is likely that operation would have to be within the first two years of life in order to give much hope of the development of good binocular vision in all except exceptional cases such as the one recorded in the present series.

SUMMARY

The state of binocular vision of 100 cases of squint in which restoration of binocular single vision was not anticipated, was assessed post-operatively.

Twenty-six per cent. developed fusion or stereopsis, the favourable factors being :—

(1) The presence of simultaneous perception before operation.

(2) Approximately equal vision in the two eyes.

(3) Age of onset of three years or more, the case being ascribed by the parents to some fever, convulsion, or shock.

(4) A small post-operative angle.

Of the cases fulfilling these criteria 76 per cent. developed fusion or stereopsis, although in most instances unsuccessful pre-operative orthoptic treatment had been given.

It appeared that those patients who were going to develop good binocular vision, did so within one year of operation.

The magnitude of the pre-operative angle of deviation and the age at operation (from six years upwards) was of no significance.

The bearing of these results upon the treatment of squint is discussed, a trial of earlier operation with careful follow-up examinations being suggested.

I wish to express my thanks to the Honorary Surgeons of the Manchester Royal Eye Hospital for permission to study their cases, and especially to Mr. O. M. Duthie for his advice and encouragement; also to Miss E. Stringer and the staff of the Orthoptic Department for the orthoptic examinations.

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THE CORNEA IN POLARISED LIGHT*
(Preliminary Communication)

BY

A. STANWORTH

MANCHESTER

THE elasticity of the cornea and sclera has aroused some interest in relationship to the regulation of the intra-ocular pressure (see Duke-Elder, 1938), but the technique of photo-elastic analysis, well known to engineers as a method of studying stresses, does not seem to have been used. On account of its transparency, the cornea is an attractive medium for such studies, especially in relation to the effects of a rise in intra-ocular pressure, and it is the purpose of this paper to describe the possibilities of the method.

THE PRINCIPLES OF PHOTO-ELASTICITY

It is not intended to describe fully the theoretical basis of the method, but merely to provide a brief summary of the relevant facts.

When the velocity of any wave-train of light is the same in all directions through a substance, the latter is said to be isotropic. Many crystalline and most organic substances are, however, anisotropic; that is, the velocity of a light-wave in them is not the same in all directions, and the substance has more than one refractive index. These substances are said to be doubly refracting, or to exhibit birefringence, and light passing through them is split, in general, into an ordinary and an extra-ordinary ray, which are plane-polarised in mutually perpendicular directions. The two wave-fronts travel at different speeds and therefore emerge with one retarded behind the other, producing a phase-difference between them.

In general a substance may be birefringent as a result of three different mechanisms :—

1. Crystalline ("eigen") birefringence, which is due to a regular arrangement of the molecules of the substance.
2. Form birefringence, due to a regular orientation of particles which, though larger than molecules, are smaller than the wave-length of light.
3. Birefringence occurring as a result of stress.

In engineering-stress analysis, a model of the structure to be studied is made in some suitable transparent material, for example celluloid, and the stresses are applied to the model, which is then

* Received for publication, April 26, 1949.

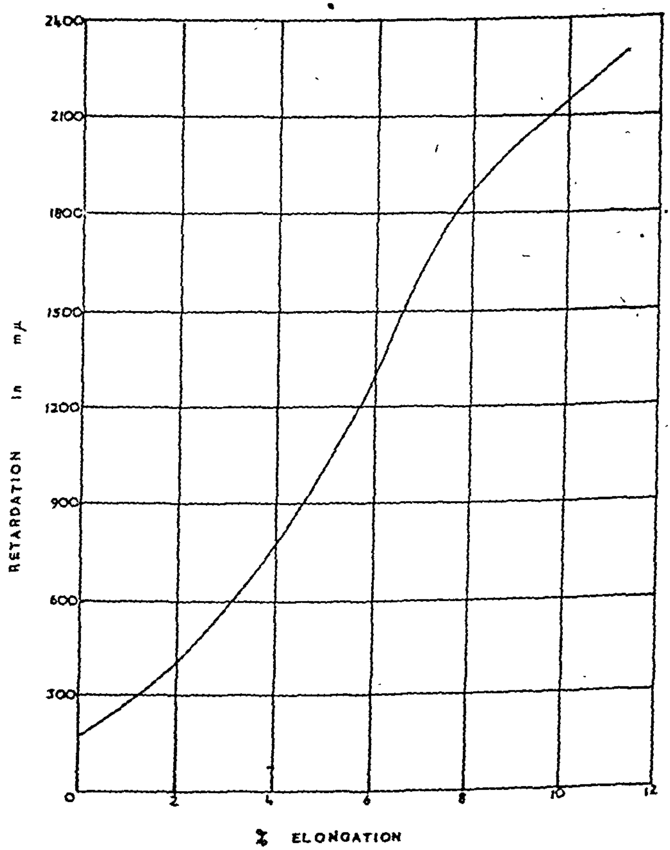
examined in polarised light, the change in birefringence at any point being a measure of the stress at that point. For the cornea no such model is necessary, because this structure can be examined directly.

Photo-elastic materials vary greatly in their sensitivity to stresses, but can be compared by means of the stress-optical co-efficient, which is given by the following formulae, adapted from Frocht (1941) :—

1. Retardation per unit thickness = Stress-optical co-efficient × twice the shearing stress applied.

2. For a strip under simple tension, Stress-optical co-efficient in brewsters =

$$\frac{\text{Retardation} \times \text{Width of strip in cm.}}{\text{Tension applied in dynes}} \times 10^{13}$$



GRAPH. 1.

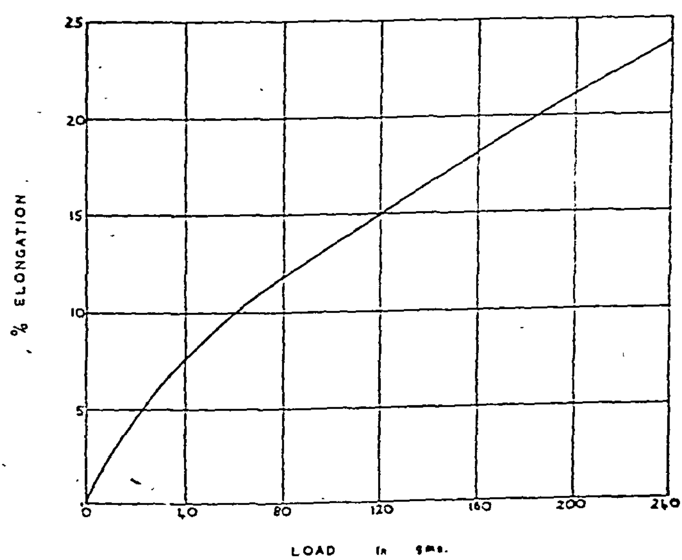
PRESENT INVESTIGATIONS

Cleanly-cut strips of cornea 1·5 mm. wide, with a small length of attached sclera at each end, were obtained from fresh cats' eyes by means of a double knife. The unstretched length was measured, and the sclera then clamped in two artery forceps. These were fixed to two pillars, the distance between which could be altered by means of a double screw, so that the cornea was elongated but its centre-point remained stationary. The distance between the tips of the forceps was measured to 0·1 mm. by means of a fine pointer moving over a scale observed through a magnifying glass.

The retardation produced by the cornea was measured at the stationary point by the method of Goranson and Adams (1933); in this way a change in retardation of 0·1 mμ could theoretically be measured, and even in biological tissues it is not difficult to measure a retardation with an accuracy of 3 mμ.

The change in birefringence with the length is shown in Graph 1, which is the average of seven strips of cornea. It will be seen that elongation of the strip produces a very rapid increase in the birefringence.

In order to calculate the stress-optical coefficient from these results, it is necessary to relate the increase in length to the applied stress. This was done by means of the autographic load-extension recorder described by Cliff (1933), Graph 2 being the curve obtained for the corneal strip described above with a rate



GRAPH. 2.

of loading of 125 gm. per minute. It will be seen that the curve forms a straight line only for relatively large loads of more than about 100 gm., producing an elongation of more than 13 per cent. For this range Young's Modulus is approximately $1{\cdot}7 \times 10^6$ dynes per sq. mm., a figure of the same order as that given by Schelske (1864). The stress-optical coefficient should be calculated only for this range, but unfortunately it is not possible to obtain accurate measurements of the retardation for this degree of elongation. The nearest approach that can be made is to take the range around an elongation of 11 per cent., when Young's Modulus is about $1{\cdot}45 \times 10^6$ dynes per sq. mm. For this range the stress-optical coefficient can be calculated, according to the formulae given above, to be approximately 1,800 brewsters. The table gives the value of this constant for some common photo-elastic materials, and it will be seen that the value for the cornea is relatively large.

TABLE OF STRESS-OPTICAL COEFFICIENTS
for light of wave-length 5461 A. (Carleton 1934.)

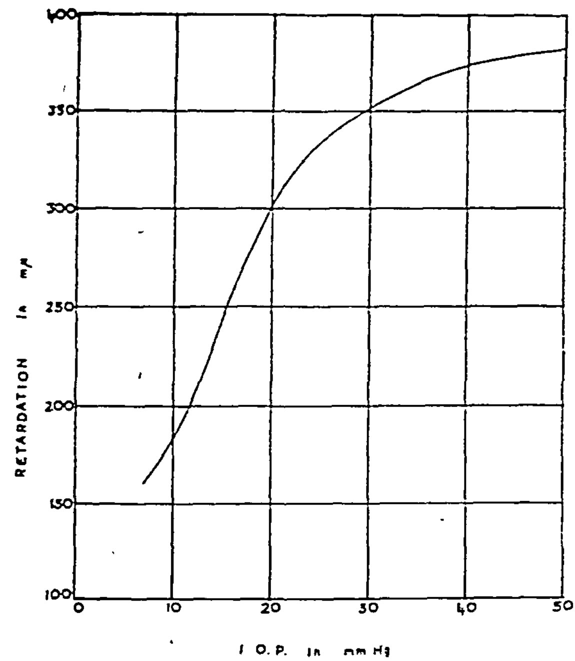
Bakelite	46.4	
Celluloid	12.8	
Glass (plate)	2.7	
Rubber (soft)	2,000	(approx.)
Rubber (hard)	106	

The range of stress over which this constant applies is well above that of the normal or even the glaucomatous eye. The stress-strain curve in Graph 2 is not sufficiently accurate for calculation of Young's Modulus over the physiological range, but it is obvious that the extensibility over the earlier part of the curve is very much greater, and the modulus therefore very much smaller, than over the higher range of applied stress. In fact Clark (1932), from observations on the increase in volume of the intact eye with increasing intra-ocular pressure, gives a value of the modulus of only about 5×10^4 dynes per sq. mm.; and since the rate of increase of birefringence with length is almost as great in the physiological as in the upper range, it would be expected that the stress-optical coefficient for the physiological range would be even larger than the value given above.

DISCUSSION

It is not possible to compare these results directly with those that would be expected in the whole eye. In the corneal strip, the increase in birefringence is produced mainly by the elongation of the lamellae running directly between the fixed ends, as those running in other directions will not be pulled upon to the same extent. In the whole eye, however, the lamellae remain curved and the applied stress is not a linear one. Nevertheless,

the corneal lamellae must increase in length as the eye enlarges with a rise in intra-ocular pressure, and for lamellae running in any one direction this would be expected to produce a change in birefringence of the same order as that given above. Assuming that the eye approximates to a sphere, and that the extensibilities of the cornea and sclera are identical, the elongation produced in such lamellae can be calculated from the graph given



GRAPH. 3.

by Ridley (1930) for the increase in the volume of the eye with a rise in intra-ocular pressure, and hence the latter can be plotted in place of the elongation in Graph 1. The hypothetical relationship thus obtained between the birefringence and the intra-ocular pressure is shown in Graph 3.

It will be seen that at physiological pressures there should be a fairly rapid increase in such birefringence with a rise in intra-ocular pressure. This change in birefringence may thus provide the basis for a method of measuring changes in intra-ocular pressure by purely optical means, but this can only be realised if a way can be found of isolating, either in whole or in part, the change in birefringence of lamellae running only in one direction, and experiments are now in progress to explore this possibility.

From Graph 3 it would appear that any such method would have its greatest sensitivity for a range of intra-ocular pressure on the low side of normal, where a change in retardation of 3 mμ corresponds on the graph to a change in intra-ocular pressure of about ¼ mm. Hg; but the exact sensitivity to be expected can scarcely be deduced from the graph owing to the large number of assumptions involved in its derivation. In fact the cornea is probably more extensible than the sclera (Schelske, 1864), and also has a different curvature, both of which factors will probably tend to increase the sensitivity by increasing the changes in lamellar length and the shearing stresses within the cornea, especially at the periphery. On the other hand, failure to isolate completely the birefringence due to lamellae running only in one direction would decrease the magnitude of any observed change in birefringence, though it may be possible to balance this by increasing the length of the pathway taken in the cornea by the light used. It is hoped that a fuller discussion of these factors, together with the experimental results, will be published later.

One further use of data regarding stress-birefringence and the stress-strain relationship is in the study of molecular structure (Schmidt, 1938; Treloar, 1947), and this too will be discussed in a further publication.

Summary

The principles of photo-elasticity are described, and the stress-optical coefficient of strips of cornea determined. The value obtained shows that the birefringence of the corneal lamellae changes rapidly with elongation of the strips, and hence also with the intra-ocular pressure. The possible use of this as a basis for a purely optical method of measuring changes in the intra-ocular pressure, and as a method of studying the molecular structure of the cornea, is described.

I wish to thank the Director of the Shirley Institute for the use of the load-extension recorder.

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HEREDITARY MYOPIA IN IDENTICAL TWINS*

BY

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THE S—. sisters are twins, aged 51 years. They suffer from high myopia inherited from their father. Both are unmarried.

Twin Diagnosis

They have been classed as identical twins because of their close resemblance both physically and mentally. Rose and May are an intelligent and cheerful pair of elderly women, indistinguishable to a stranger. They have often had the same illnesses at the same time, they object to being parted, and they tend to answer questions in unison.

They went to school at about the age of five, always had to sit close to the blackboard, and were not allowed to do needlework. At about that time they were first examined and found to be myopic. They had measles together at the age of seven. Shortly after that, both started to wear glasses, and still do so.

Certain characteristics were examined in detail, with the following results:—

Hair. Exactly the same as regards quantity, quality and colour. The crown whorls were mirror images of each other.

Eyebrows. Thickness, hair whorl and distribution were identical, distance between the inner ends 2 cm. in each case.

Teeth. Rose has six false teeth — three on each side above May has seven — four lower central incisors and three upper teeth The remaining corresponding teeth resemble each other closely.

Noses. Identical in shape.

Eyes — Iris. The colour and structure of the irides are identical, including a small radial yellow streak at five o'clock in the right eye, which could only be seen with the lens and loupe.

Lens. No opacities in either.

Vitreous. Rose (R) Large snaky opacity. (L) Small snaky opacity. May (R) Vitreous clear. (L) Numerous snaky vitreous opacities.

Fundi. The fundi, although not identical as regards vascular pattern and the characters of the disc, resemble each other very closely. The most noticeable difference was the presence of spontaneous venous pulsation in both eyes in the case of Rose, and its absence in the case of May.

The common fundus picture, equally developed in all four eyes, was as follows:—

(1) High myopia at the posterior pole — moderate only at the periphery.

(2) Extensive choroidal atrophy of the posterior pole — much less marked at the periphery. Large myopic crescents surrounding the disc but falling short of the macula.

(3) Marked pigmentary mottling at the macula.

(4) Vessels narrow and irregular. No other sign of arterio-sclerosis apart from moderate crushing at venous crossings.

(5) No haemorrhages or exudates.

* Received for publication, January 21, 1949.

MEASUREMENTS

(1) *Ocular.*

(a) *Refraction* under homatropine and cocaine.

Rose :— (R) $\dfrac{-22.0}{+1.5\downarrow 95^\circ}$ (L) $\dfrac{-15.0}{+2.0\swarrow 80^\circ}$

May :— (R) $\dfrac{-22.0}{+1.5\downarrow 90^\circ}$ (L) $\dfrac{-24.0}{+6.0\searrow 100^\circ}$

(b) *Visual acuity*: was only tested for near vision.

Rose :— (R) without glasses. Reads J6.
(L) without glasses. Reads J1.

May :— (R) without glasses. Reads J1.
(L) without glasses. Reads J1.

	Rose	*May*
Interpupillary distance	55 mm.	55 mm.
Horizontal measurement of palpebral fissure — inner to outer canthus ...	(R) 25 mm. (L) 25 mm.	(R) 25 mm. (L) 25 mm.
Vertical measurement of palpebral fissure in normal distance gaze ...	(R) 11 mm. (L) 11 mm.	(R) 11 mm. (L) 11 mm.
Intra-ocular pressure (Schiötz) ...	(R) 16 mm. Hg. (L) 17 mm. Hg.	(R) 15 mm. Hg. (L) 17 mm. Hg.

(2) *Other.*

Circumference of head	51 cms.	50.5 cms.
Glabella to external occipital protuberance...	32 cms.	32 cms.
Height	145 cms.	144.5 cms.
Tip of olecranon to ulnar styloid ...	(R) 23 cms. (L) 23 cms.	(R) 23 cms. (L) 23 cms.
Blood pressure	160/70	158/80

The only significant difference is in the refraction. The right eyes correspond closely, but between the left eyes there is a difference of 9 D. spherical, 4 D. cylindrical, and 20° in the axes of the cylinders. If the eyes are considered as mirror images, then the greatest difference between corresponding eyes is 7 D. spherical — *i.e.*, between May's right eye and Rose's left. In either case, Rose shows 5 D. more anisometropia than May, and this probably accounts for the relatively poor visual acuity in her right eye.

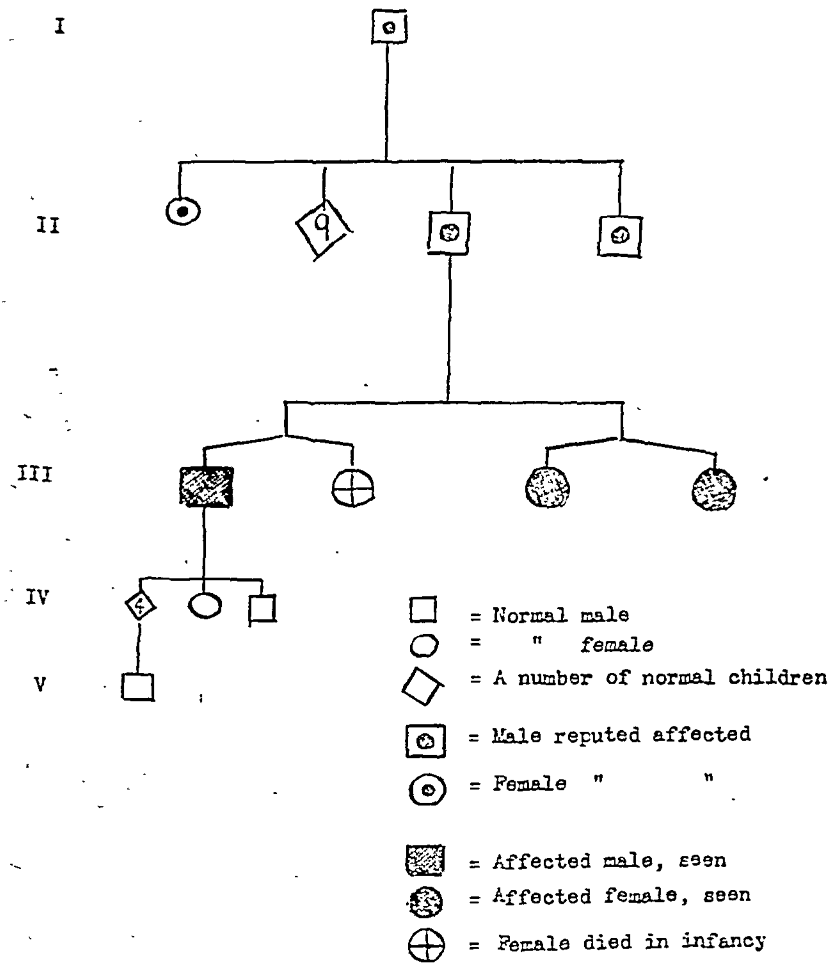
Pedigree

The parents were not related. Both the father and paternal grandfather are reputed to have had severe short-sight. One paternal uncle and one paternal aunt are also reported to have been affected. None of the mother's relatives was known to be affected.

The patients' sibship consisted of two pairs of twins, of which the elder pair was dizygotic. The sister died in infancy from an

unknown cause. The brother is alive and is myopic; he has six children and one grandchild, all apparently normal. Apart from the twins Rose and May, the only other members of the family examined have been the brother George S. and two of his children.

PEDIGREE OF S. FAMILY



George S. Aged 48 years. Metal machinist.

Both eyes are myopic, but in his case the right eye is markedly, and the left noticeably, less severely affected than in his sisters. With his right eye corrected, he is able to carry on his job, which demands considerable precision. The left is amblyopic.

Refraction under homatropine.

$$\text{(R)}\quad \frac{-5.0}{+2.0\angle 65^\circ} \qquad\qquad \text{(L)}\quad \frac{-15.5}{+1.5\angle 65^\circ}$$

Fundi. (R) There is a small myopic crescent limited to the temporal and inferior aspects of the disc, no myopic degeneration, a normal macula, and normal vessels.

(L) There is high myopia with considerable choroidal atrophy limited to the posterior pole. The periphery is much less myopic and shows no degeneration. There is a large myopic crescent enveloping the disc and falling just short of the macula, which itself shows pigmented mottling similar to that of the twins. The vessels are normal.

The left fundus is in fact a milder example of the same condition as that of the twins.

The two children examined, Robin and Jean, aged 10 and 12 years respectively, have normal vision. The fundi are normal. Robin has slight hypermetropic astigmatism, and Jean's refraction under homatropine is (R) -1.0 D, (L) -0.5 D. The remaining children could not be examined. One is training at a Police College, and the other three were said to have normal sight. Apparently none of George S.'s descendants has high myopia.

Discussion

The occurrence of high myopia in identical twins with a pedigree showing direct transmission over three generations is evidence of its genetic origin.

The lesion is equally developed in all four fundi, which correspond closely. The refractions, however, do not. Such differences of refraction in monozygotic twins with high myopia are well recognised (Bücklers, 1939; Marchesani, 1935). They suggest that, while the general picture of high myopia in these cases is genetically determined, the exact type and degree of refractive error may perhaps be influenced by environmental factors.

In view of the clearly dominant type of transmission, one would have expected the condition to reappear in the six children of George S. That it has not done so emphasises the variability of transmission in an undoubtedly genetic condition.

Acknowledgements

I wish to thank Mrs. M. H. Edwards of the Metropolitan Society for the Blind, and Mrs. Helena Simpson, Matron of Armitage House, Worthing, for their kindness and co-operation in giving me the opportunity to see these cases.

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TRAUMATIC OR "CONCUSSION" CHRONIC GLAUCOMA*

BY

ARTHUR D'OMBRAIN

SYDNEY

THIS paper is based upon the observation of a series of cases of monocular chronic glaucoma of traumatic origin, and it is suggested that there exists a type of chronic glaucoma hitherto inadequately recognised as a specific clinical entity, characterised by uni-ocular incidence and a history of concussional trauma. It is contended that this chronic glaucoma is one of the several possible results of concussion of the ocular bulb, and that production of this type of glaucoma is a chronic process initiated by trauma, causing a gradual and progressive blockage of the endothelium-lined spaces of the trabecular region by a sclerotic, degenerative or proliferative lesion. It is proposed to summarise and extend views expressed in previous communications on this subject in 1944 (1), 1945 (2), and 1946 (3), in other journals.

Before presenting a selection of case-histories—many of which were kindly sent to me by colleagues—and before considering what conclusions may reasonably be drawn from them, I will describe the case which first drew my attention to the possibility of uni-ocular type of chronic glaucoma.

In March 1940 I was consulted by a man aged 28 years, who told me that his right eye had been going misty for some months. On examination the right pupil was semi-dilated, and reacted only sluggishly to light, the right disc was cupped, and the intra-ocular tension was 40 mm. Hg. There was a moderate contraction of the right nasal visual field, and vision was 6/9. The anterior chamber was of normal depth. The left eye, in which vision was 6/5, appeared normal, but following orthodox procedure in cases of primary chronic glaucoma, I treated both eyes with eserine sulphate ¼ per cent. As the intra-ocular tension in the right eye under eserine, even when this drug was used in increasing frequency, never fell as low as 30 mm. Hg, and as the vision continued to appear misty to the patient, I trephined the right eye in July 1940. The tension fell to 20 mm. Hg, at which level it remained for six years.

Acting on the assumption that primary chronic glaucoma is a bilateral disease, I kept the left eye under eserine for ten months. In May 1941, after once again taking the vision, tension and visual field of the left eye, and finding no abnormality in these, nor in the appearance of the optic disc, I concluded that I might have been too ready to accept this case as one of ordinary primary glaucoma, and I did what I should have done at the outset (and what I have never since omitted to do), namely, take a careful history. I then found that eighteen years earlier, this man had fallen from a horse and injured the right side of his face. I made him ask his parents about this accident, as he was only ten at the time of its occurrence. His mother remembered it clearly, because the accident had greatly alarmed her; and she stated that his right eyelids remained swollen for many days. Evidently

* Received for publication, March 28, 1949.

a large haematoma ensued. I took the risk of discontinuing treatment in the left eye, and for the six years during which I subsequently observed this patient, no sign or symptom of glaucoma appeared in this eye.

TABLE I

Case	Age	History	Signs	Treatment
1 Mr. P. W.	28 11/3/1940	Right eyesight had gone misty.	Right eye: Pupil sluggish and larger than left pupil; intraocular tension 40 millimetres of mercury; vision 6/9; visual field: basal contraction small with Ronne's step. Left eye: Normal in all respects.	Eserine both eyes until July, 1940, when right eye was trephined successfully, bringing the tension down to 20 millimetres of mercury. Left eye kept under eserine until May, 1941, when a history was elicited of a severe blow on the right eye from a fall 18 years previously. Eserine discontinued left eye, which was still normal in April, 1945.
2 Mr. H.M.	61 15/11/1940	Right vision falling for past twelve months. Past multiple infections of both syphilis and gonorrhœa. Was once a sailor.	Right eye: All the signs of acute congestive glaucoma. Left eye: Tension normal, but disseminated chorioiditis present. Left visual field full except for scotomata corresponding to the patches of chorioiditis.	Miotics until right eye quiet; then operation with a mechanical trephine. Tension reduced to 20 millimetres of mercury, but cataract developed later. Left eye kept under miotics for three and a half years, until June, 1944, when a history was elicited of seventeen fights, many falls (one causing a fracture of the skull), and blows on the face from bottles in tavern brawls and arguments with women. All treatment stopped. Left eye still normal in June, 1945.
3 Mr. J. W.	63 26/6/1942	Condition previously diagnosed as glaucoma by one doctor and as cataract by another. Using pilocarpine at night in the affected left eye.	Right eye: Normal in all respects. Left eye: Cupped disk, 40 millimetres tension, nasally contracted field with large Rönne's step. Left vision less than 6/60.	Eserine both eyes. In August, 1942, history elicited of injury to left eye from fall from a horse; lids had sutures inserted. Treatment stopped right eye in March, 1943. Right eye still normal in April, 1944. Not seen since.

This case appeared to me of unusual interest, for although acute congestive glaucoma secondary to trauma is well known, nowhere could I find any definite record of chronic glaucoma subsequent to and caused by trauma, except from lens luxation. Moreover, the long period between the injury and the onset of symptoms seemed peculiar, to say the least, and almost made me forsake the theory of cause and effect. However, as case followed case, I began to feel that the matter was worthy of comment, and when, after my first short communication on the subject,[1] other oculists began to send me details of similar cases, I felt encouraged to follow up the trail, and have since read two papers before the Ophthalmological Society of Australia.[2, 3]

Many of my colleagues thought that I had made an observation of some value; others were doubtful that such a variety of traumata could produce so constant a lesion especially, as in many of the

cases, after so long a period of time. Therefore I have now set out the matter in some detail, for if there is indeed such a clinical entity as traumatic uni-ocular chronic glaucoma, or, as I now name it, concussion glaucoma, issues of medical and medico-legal importance are raised.

One issue of medical importance is this: if, as a result of concussional trauma to one eye, or affecting one eye, a state of chronic glaucoma is set up in that eye, there is no need to fear an onset of glaucoma in the other eye, nor any need to treat the other eye. The other and wider medical corollary is, that if so simple a factor as concussional trauma can initiate a chronic glaucomatous process, then primary simple non-inflammatory glaucoma may be in essence more truly simple in nature than the multiple theories of its genesis would suggest.

The issue of medico-legal import is, of course that of compensation, either civil or military, for uni-ocular chronic glaucoma resulting from trauma.

In reviewing this series of cases, comment will be made under four headings:

1. The nature of the lesion.
2. The nature of the causative traumata.
3. The probable aetiological mechanism.
4. General conclusions and comments.

1. The Nature of the Lesion

First, in these cases we are confronted, not with the well-recognised condition of traumatic acute congestive glaucoma — though a congestive state may become a terminal stage—but with a true, chronic, progressive non-inflammatory glaucoma which may incidentally exhibit the signs and symptoms of sub-acute attacks, namely rainbow haloes, attacks of pain and blurred vision.

Secondly, almost without exception, a remarkable feature of these cases is a delay in the onset of symptoms, the period of delay ranging from a few weeks to many years after the date of injury. This is not necessarily to say that the start of the glaucomatous process has been delayed; it may merely indicate the delay in discovery by the patient of the symptoms of a chronic and insidious disease. What this delay in the onset of symptoms does emphasize, is that no gross visual upset occurred at the time of injury, in contradistinction to the immediate signs and symptoms seen in cases of acute congestive glaucoma due to gross trauma.

Thirdly, the lesions in this series are uni-ocular, and remain so over long periods of time, in contradistinction to primary non-traumatic chronic glaucoma, which is almost invariably bilateral sooner or later.

2. THE NATURE OF THE CAUSATIVE TRAUMA

Analysis of the cases shows three groups of injuries. These are :—

(*a*) Blows upon the eye itself.

(*b*) Injuries to the skull, mostly causing either a fracture of the bone or a concussion of the brain.

(*c*) Heavy falls, as from a horse or vehicle, or from a height of some feet.

Looked at as a group, these injuries can be regarded as various forms of concussion, and I would suggest that these glaucomatous conditions represent one of the several possible results of concussion of the eyeball. With other possible results everyone is familiar, *e.g.*, striation of the cornea, mydriasis, dislocation of the lens, cataract, irido-dialysis, detachment of the retina and intra-ocular haemorrhage.

Some of those lesions may produce a condition of acute congestive glaucoma. I am suggesting that, in addition to such well-known possible results of concussional trauma, another should be added, namely, the initiation of chronic glaucoma.

3. THE PROBABLE AETIOLOGICAL MECHANISM

How is it that an injury not sufficient to cause an attack of acute congestive glaucoma, could be conceived of as initiating chronic glaucoma? I believe that these cases display the effects of concussion, effects produced either by direct trauma to the cornea or by the pressure of suddenly compressed aqueous humour. Presumably the lesion is in the region through which the aqueous filters away from the anterior chamber, namely in the trabecular meshwork of the cornea adjacent to Schlemm's canal; and I interpret the lesion either as a fibrosis or as a cuticular proliferation ("glass membrane") similar to that recorded by several workers, notably Reese (1944)[4].

Such an hypothesis, envisaging as it does a chronic lesion, be it fibrotic or degenerative or proliferative, offers an explanation of the remoteness in the time of the history of injury in so many cases. It would also explain the cases due to indirect trauma, such trauma being of a nature to cause a concussional shock to the eye.

4. GENERAL CONCLUSIONS AND COMMENTS

These cases present three factors in common:

(*a*) A history of concussional trauma.
(*b*) Glaucoma in one eye.
(*c*) A non-glaucomatous other eye.

It would appear, then, if these cases are in truth traumatic in origin, that some types of concussion-shock can upset the intra-ocular pressure stabilisation, either by the mechanism I have postulated or in some other way. Similarly, some cases of bilateral chronic glaucoma may be of traumatic origin. However that may be, these cases offer evidence that chronic glaucoma can be caused by trauma, and that such cases show not a static or temporary rise in the intra-ocular pressure, but rather a progressive chronic glaucoma non-inflammatory in type, though some cases display terminal inflammation.

A search of ophthalmic literature only reveals brief and scattered allusions to the possibility of such a lesion. In most accounts and discussions on glaucoma the existence of traumatic chronic glaucoma is not even considered and it would seem that this clinical entity has been missed. If so, why? The omission is explained by the way in which glaucoma has traditionally been presented to us in the text-books. These books divide *primary* glaucoma into two broad groups—namely acute congestive and chronic, but *secondary* glaucoma receives no such grouping. Instead of that we find a long list of causes, among which trauma is mentioned only as a cause of the acute congestive type. A classification of secondary glaucoma into the same two fundamental groups, acute and chronic, might be worth while, for there are other causes of *secondary* chronic glaucoma besides trauma, *e.g.*, chronic uveitis, intumescence and subluxation of the lens, Morgagnian cataract, intra-ocular tumour, epidemic dropsy and hydrophthalmia.

Duke-Elder[5] has a chapter in his Text Book of Ophthalmology on glaucoma secondary to trauma, but it is evident that what is envisaged is a congestive lesion. He states: "The primary mechanism is undoubtedly an upset of the local nervous control of the circulation, any disturbance of which is generalised over the entire uveal tract by axon-reflexes. Such a disturbance produces a vascular instability with dilation of the capillaries, engorgement of the circulation, stasis and oedema, a mechanism, indeed, comparable to that which occurs in inflammatory glaucoma."

Posner and Schlossman[6] (1948) give a list of *nineteen* eye conditions associated with primary glaucoma, *forty* general diseases

associated with primary glaucoma, and *twenty-four* causes of secondary glaucoma, the twenty-fourth heading being "Unknown Aetiology." Nowhere in these long lists is concussional trauma mentioned, nor indeed any trauma except perforating wounds, traumatic cataract and dislocation of the lens, and even these three applied to glaucoma as a whole and not specifically, if at all, to chronic simple glaucoma.

The only unmistakable reference to the possible rôle of trauma in the production of a chronic glaucoma, that I have been able to find, is by Reese[4] (1944). In his summing-up Reese states: "This (cuticular product) may occur as a primary disease with no apparent provocation. It may also occur as a result of inflammation in the anterior chamber or as the result of trauma to the eye." He does not say what kind of trauma, nor does he give any detail of traumatic cases beyond stating that a history of trauma was regarded as a significant factor in six of his twenty-six cases. Reese omitted sixteen other eyeballs with deep-chamber, wide-angle glaucoma, in which the glaucoma was obviously due to obstruction of the trabeculae from sclerosis and not to the formation of a "glass membrane." Here, then, were forty-two cases of glaucoma from trabecular obstruction of one form or another, some of them with a history of trauma.

Conclusion

1. We should not too hastily diagnose every case of chronic glaucoma in one eye as a primary and therefore eventually bilateral disease, for, upon taking a careful case-history, we may find it to be a lesion affecting only one eye, and in origin secondary to concussional trauma.

2. Probably some cases of bilateral chronic glacouma may have their origin in the shock of a concussional trauma.

The three tabulated cases are selected from a group of 37 observed by myself or by colleagues.

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BILATERAL SYMMETRICAL TUBERCULOUS ULCERS OF THE BULBAR CONJUNCTIVAE TREATED WITH STREPTOMYCIN

BY

B. K. DAS GUPTA

and

M. USMAN

CALCUTTA

TUBERCLE of the conjunctiva is a rare condition. It occurs chiefly in young people between the ages of 20 and 30, and assumes various forms, possibly by reason of difference in the virulence of the infection, and difference in individual resistance. Clinically five types are recognised, but sometimes various forms are found combined.

CLINICAL TYPES

(1) Ulcerative type—characterised clinically by the presence of one or more miliary ulcers, which may or may not coalesce. They are usually found on the palpebral conjunctiva, rarely on the bulbar conjunctiva.

(2) Nodular type—characterised by small greyish subconjunctival nodules, which are very difficult to differentiate from trachomatous granules.

(3) Hypertrophic papillary type—characterised by outgrowths of granulation tissue, which usually arise from the fornices, sometimes from the tarsal conjunctiva. Sometimes they become pedunculated and project on to the surface forming cock's-comb excrescences, which frequently show superficial ulceration.

(4) Polypoid type—pedunculated tumours arising from the tarsal conjunctiva.

(5) Tuberculoma—hard solid subconjunctival nodules in the bulbar conjunctiva, which do not undergo ulceration. The conjunctival epithelium remains intact, while the rest of the conjunctiva remains normal.

MODE OF INFECTION

Most of the cases are probably endogenous and therefore secondary, others are exogenous and primary. When primary, the infection is carried from outside, e.g., by particles of sputum or dust bearing tubercle bacilli. There may be a breach of the mucous membrane from trauma, and the abraded surface is infected with tubercle bacilli. Occasionally the conjunctiva is

affected by direct extension of lupus from skin or nose, or from adjacent tuberculous disease of the sclera, ciliary body or choroid.

CASE REPORT.

Patient A. K. D., 21, Hindu, male, a resident of Midnapore (Bengal), cultivator by occupation, came to the out-patient department of the Eye Infirmary, Medical College Hospitals, Calcutta, on June 9, 1948, and was admitted under the Professor of Ophthalmology on June 12, 1948, for symmetrical conjunctival ulcers of both eyes, involving the bulbar conjunctiva.

Present history. One year previously, he had noticed oedema of both lids with considerable epiphora and photophobia. Two months later, epiphora was much less in the left eye but there was considerable discharge from it throughout the day. Three months after, he noticed a shallow ulcer in the left eye just below the cornea. In the right eye he started getting muco-purulent discharge eight months later. He never noticed any ulceration in the right eye.

Family history. Parents are alive and healthy. He has two brothers and two sisters, all of them healthy. He is unmarried and there is no history of contact with any tuberculous individual.

History of past illness. The patient had an attack of malaria 3 years previously and was cured in three months. He had an attack of dysentery 2 months previously. While in hospital he had a relapse. He gives a history of haemoptysis once, and that occurred about a month and a half before the eyes became affected. For 8 days he had streaks of blood with the sputum, and also had epistaxis at that time. He does not give any history of evening rise of temperature, night sweats or loss of appetite and weakness.

Diet. He lives on an average Bengali diet consisting of rice, dal, vegetables, fish and milk. Occasionally he takes meat and fruits.

Examination of the case at the time of admission.

The patient was rather thin. Both palpebral fissures were narrowed.

In the right eye the bulbar conjunctiva was extremely congested. Below the cornea there was an oval ulcerated patch ¾in. x ½in. with well-defined margins. The floor of the ulcer had involved the sclera. On the surface of the ulcer there was a whitish discharge. Cornea was clear. There were no k.p. Pupil active to light. Tension normal. Vision 6/12. Fundus healthy.

In the left eye the condition was the same, except that the ulcer was bigger and deeper than in the right eye. The erosion of the sclera was greater, and uveal tissue could be seen through the floor of the ulcer. The lower part of the cornea was involved in the ulcerative process. Vision 6/18. No pathological changes seen in the fundus.

No glandular enlargement was detected. Examination of heart and lungs did not reveal any pathological lesions.

Temperature was recorded for 7 days and no rise was detected at any time of the day or night.

Investigations and treatment.

On June 23, 1948, he had an attack of dysentery.

Stool examination report:—

Reaction	Acid
Pus cells	+
R.B.C.	+ +
Mucus	+
Blood	+
Epithelial cells	+
Entamoeba histolytica	+ +
Ova of ankylostoma duodenalis	+
Larvae of strongyloides stercoralis	+
Vegetable cells	+ +
Occult blood reaction	+

FIG. 1. Showing the ulcers at the time of admission. Picture drawn on June 12, 1948.

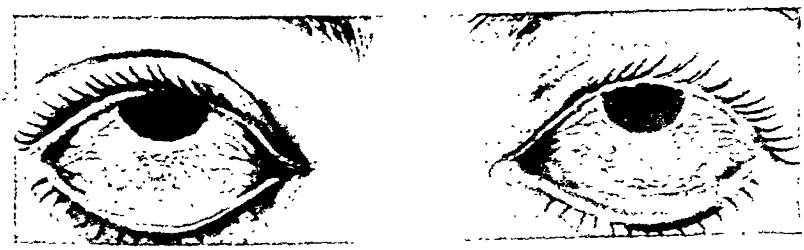

FIG. 2. Six days after streptomycin treatment. Picture drawn on July 30, 1948.

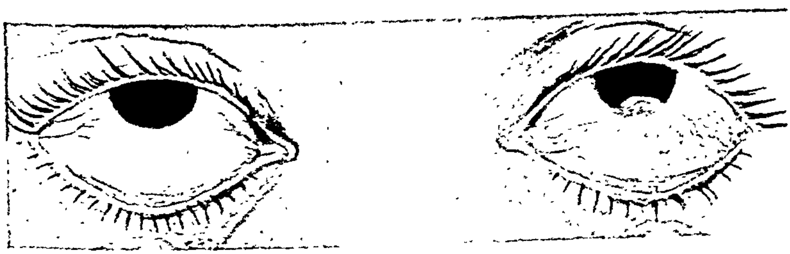

FIG. 3. Twenty-four days after streptomycin treatment. Picture drawn on August 18, 1948.

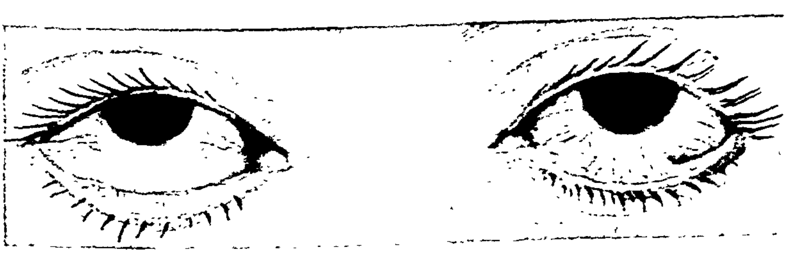

FIG. 4. The condition of the conjunctiva on September 2, 1948.

He was treated with emetine hydrochloride injections followed by enterovioform tablets, and the dysenteric infection was cured.

On June 26, 1948 discharge from the floor of the conjunctival ulcers was sent for culture, and scrapings for any acid-fast bacillus. The culture was found to be sterile. Scrapings revealed presence of acid-fast bacilli.

On June 28, 1948 patient was sent to the chest department for Mantoux test and skiagram of the chest. The Mantoux test was + + with 10,000 dilution, which suggests that his reaction was of high intensity. Screen examination showed no lung infiltration; this was corroborated later by skiagram of the chest.

On June 29, 1948 a section of the conjunctiva from the edge of the ulcer was taken and submitted for histological examination. Section showed heavy infiltration of the subepithelial layers with round cells, and a few typical tubercular giant-cell systems with epitheloid cells.

On June 29, 1948 a smear was taken again for A.F.B. and found to be positive.

On July 2, 1948 his total and differential blood count was done, and sedimentation rate was estimated.

Blood picture:—

Total W.B.C. ...	7500 per c.mm.
Poly.	59 per cent.
Lympho.	20 per cent.
Large mono.	2 per cent.
Eosinophil	19 per cent.
No M.P. seen.	
W.R. and Kahn ...	Negative.
Sedimentation rate ...	40 mm. per hour (Westergren method).

The centrifugalised deposit of urine was examined for acid-fast bacilli on June 30, 1948, but none was found.

Treatment.

When the patient first came under treatment, his eyes were washed with normal saline, and penicillin drops (1500 units per c.c.) were instilled every hour without benefit. The ulcers were cauterised with pure lactic acid 3 times, but results were disappointing.

On July 24, 1948 streptomycin treatment was started locally and perenterally. 1 gm. of streptomycin was dissolved in 2 c.c. of distilled water, and drops were put in each eye every hour from 8 a.m. to 8 p.m. each day. For injection, 1 gm. of streptomycin was dissolved in 2 c.c. of pyrogen-free distilled water, and was injected intramuscularly deep into the gluteal region.

July 24, 1948,	6.30 p.m.	1 gm. streptomycin
July 25, 1948,	9.00 a.m.	1 gm. streptomycin
	6.00 p.m.	1 gm. streptomycin
July 26, 1948,	8.15 a.m.	1 gm. streptomycin
	7.00 p.m.	1 gm. streptomycin
July 27, 1948,	8.00 a.m.	1 gm. streptomycin
	6.30 p.m.	1 gm. streptomycin
July 28, 1948,	8.00 a.m.	1 gm. streptomycin
	7.00 p.m.	1 gm. streptomycin
July 29, 1948,	8.00 a.m.	1 gm. streptomycin
July 30, 1948,	8.00 a.m.	1 gm. streptomycin
July 30, 1948,	ulcer in the right eye healed considerably.	
July 31, 1948,	8.00 a.m.	1 gm. streptomycin I.M.

July 31, 1948, smear examination from the ulcers did not reveal the presence of any acid-fast bacillus.

From August 1, 1948 to August 17, 1948, each morning at 8 a.m. the patient had 1 gm. of streptomycin intramuscularly.

From August 1, 1948, streptomycin drops were stopped in the right eye, but were continued in the left eye every hour.

From August 5, 1948, streptomycin drops were given at a strength of 0·01 per cent. solution until August 13, 1948. The ulcers seemed to remain static, so previous strength was resorted to, *i.e.*, 1 gm. of streptomycin in 2 c.c. of distilled water.

REMARKS

Altogether 29 gm. of streptomycin were injected, and 7 gm. were used as drops. It was found that at first, with streptomycin, the ulcers cleared up rather rapidly, but after some time they became static, and when streptomycin was stopped, the healing process proceeded rapidly. We always remembered the complications which might follow large doses of streptomycin, and were very cautious in administering it. When the ulcers were completely healed there was slight symblepharon in each eye.

The illustrations were drawn on days noted against each of them. Microphotographs of the section are seen in Figs. 5 and 6.

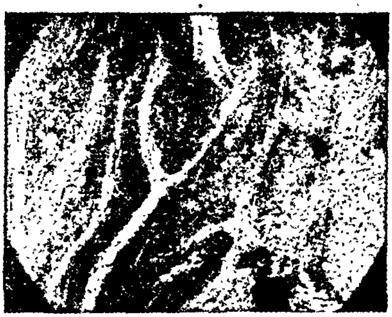

FIG. 5.

Microphotograph of the section taken from the edge of the conjunctival ulcer—low power.

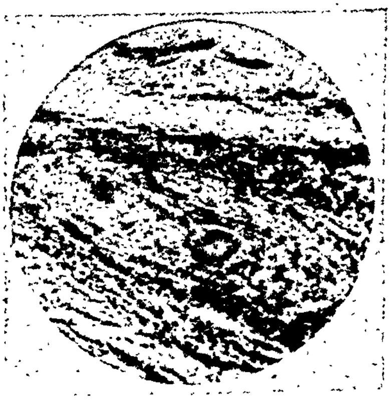

FIG. 6.

Microphotograph of the section taken from the edge of the conjunctival ulcer—high power magnification showing typical tuberculous giant-cell system with epithelioid cells and round cell infiltration.

SUMMARY

1. A case of bilateral tuberculous ulcer of the bulbar conjunctiva treated with streptomycin is described.

2. There was no response to penicillin therapy or lactic acid cauterisation.

3. The ulcers responded marvellously with streptomycin applied locally and parenterally.

4. There was no untoward complication after streptomycin therapy.

5. High concentrations of drops seem to have a better effect than low concentrations.

6. The ulcers seem to progress more favourably if the injections and drops are discontinued for some time after a few days of treatment.

7. After 7 days of treatment with streptomycin, scrapings from the floor of the ulcers failed to reveal the presence of any acid-fast bacilli.

8. Sedimentation rate dropped from 40 to 10 mm. per hour after streptomycin treatment.

Acknowledgment. We are very grateful to the Superintendent, Medical College Hospitals, Calcutta, for allowing us to publish this case. We are also indebted to Dr. P. K. Sarkar, Pathologist to the Eye Infirmary, Medical College Hospitals, Calcutta, who did the microscopic sections; to the artist of our institution, Mr. A. Das Gupta, who has kindly drawn the pictures; to Prof. B. P. Trivedi, for helping us to take the microphotograph; and to Dr. B. P. Neogy, of the Jadavpur Tuberculosis Hospital for valuable suggestions during the treatment of this case.

THE PHOTOPIC LUMINOSITY CURVE AND VISUAL PURPLE

BY

L. C. THOMSON

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RECENTLY Dartnall has suggested that the photopic as well as the scotopic luminosity may be mediated by the single pigment visual purple. He has deduced the shape and spectral position of the photopic luminosity curve of the eye by calculating the effect of an accumulation of indicator yellow upon the spectral distribution of the light absorbed by visual purple. He finds that the effect of increasing indicator yellow concentration is not, as might be

expected, a steady displacement of the maximum of the curve towards red wavelengths, but that a *limiting* position is rapidly reached. The calculated luminosity curve corresponding to this limiting position agrees with the C.I.E. standard photopic curve.

Thus it would appear that the photochemical activity upon which the sensation of photopic luminosity is based relates to one substance only, namely, visual purple. If this be true, however, we are forced to the unlikely conclusion that the mechanisms responsible for hue discrimination make no contribution to the overall sensitivity of the light-adapted eye. In other words Dartnall's hypothesis leaves no room for a luminosity contribution from any photo-sensitive substance other than visual purple, since the photopic sensitivity of the eye is, apparently, *completely* explained by supposing that it is mediated by a single substance, visual purple.

Thus the agreement between the derived curve and the photopic luminosity function, upon which the hypothesis basically relies for its verification, leads to the difficulty that the colour discrimination of the light-adapted eye cannot be easily explained.

On examination, however, the correspondence is seen to depend upon (*a*) the choice of the C.I.E. standard curve to represent the photopic sensitivity of the average eye, and (*b*) a correction applied to the data to allow for the absorption of light by the yellow macular pigment.

(*a*) In 1924 Gibson and Tyndall measured the foveal photopic luminosity curve in 56 subjects and found that for wavelengths shorter than 500 $\mu\,\mu$ their own mean curve showed departures, which were outside their experimental error, from the then existing American standard curve (I.E.S.). In recommending a new standard curve they did not, however, suggest any change in the region below 500 $\mu\,\mu$, so that the present standard curve which is based upon Gibson and Tyndall's recommended figures still shows the departures from their mean results.

The extent of the departures may be seen in Fig. 1. Here log. luminosity (sensitivity) is plotted against the wavelength, and both Gibson and Tyndall's mean curve and the present C.I.E. standard curve are shown, when corrected by means of Ludvigh and McCarthy's data, to allow for the (pre-retinal) absorption of light in the optical system of the eye. The curves may therefore be regarded as a measure of the retinal, as distinct from the corneal, sensitivity. The data are for an equal quantum intensity spectrum. The curve marked G and T (C.F.S.) is for one of Gibson and Tyndall's more sensitive observers; that marked W.D.W., a sensitivity curve measured recently with the Wright colorimeter at Imperial College; both similarly corrected.

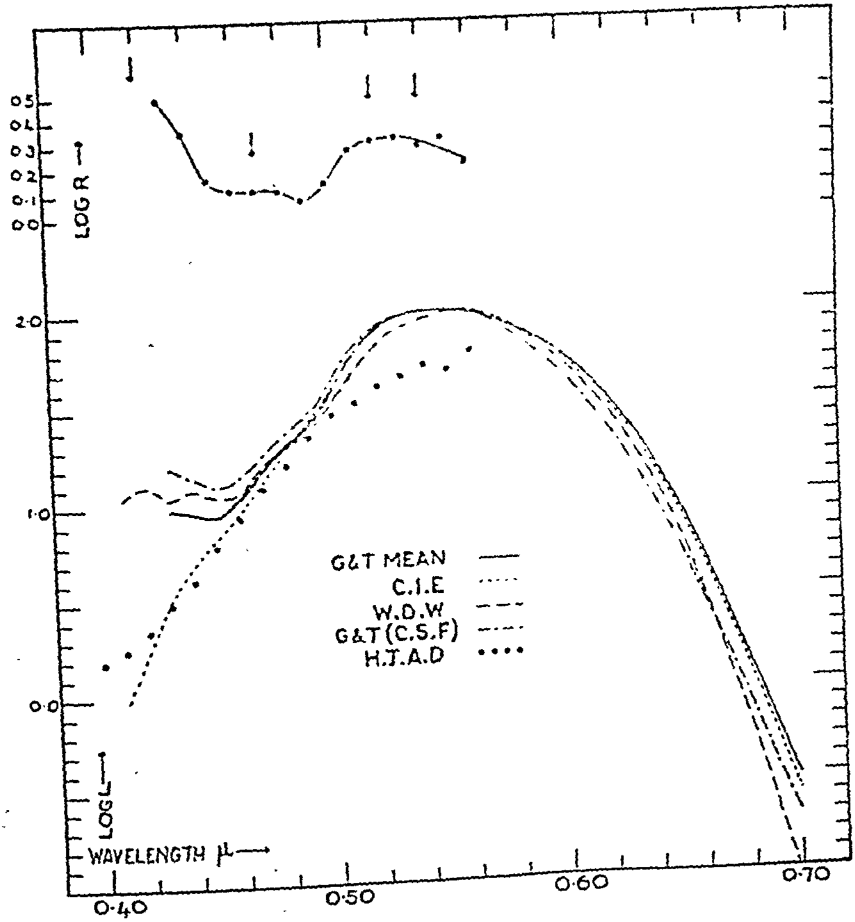

FIG. 1.

G & T Mean ...	Mean sensitivity of the eye as measured by Gibson and Tyndall.
C.I.E.	The present standard photopic curve.
G & T (C. F. S.)	The sensitivity for one of Gibson and Tyndall's observers.
W.D.W. ...	The sensitivity of one observer measured recently.
H.J.A.D. ...	Dartnall's derived curve, but without correction for macular absorption.

The arrows above the uppermost curve indicate the spectral regions in which modulator activity has been demonstrated.

Thus the curve chosen by Dartnall, the C.I.E. curve, although "standard" in the sense that it is internationally agreed, does not, in fact, represent the average sensitivity of the eye below 500 $\mu\mu$.

(*b*) Polyak has stated that the yellow macular pigment lies in the ganglion and bipolar layers of the retina, and since the light does not traverse these layers to reach the foveal centre, and only to a small extent to reach a point displaced by 1°, it would seem that measurements of sensitivity made with a 2° field (such as Gibson and Tyndall's), would be little affected by this pigmentation. Thus it would perhaps be more appropriate to omit a correction for macular pigment absorption. Dartnall's uncorrected ratios from Table I of his paper have, therefore, been plotted in Fig. 1. The set of points has been lowered to bring the point at 490 $\mu\mu$ below Gibson and Tyndall's mean curve, and it can be seen that the agreement between the derived curve and the C.I.E. curve is in large measure dependent upon the macular pigment correction.

The factor by which the mean sensitivity of the eye (G. and T.) is greater than that derived by Dartnall is shown in the upper part of Fig. 1. This curve is a measure of the failure of the derived curve to describe the mean photopic sensitivity of the eye.

Are we then to discard Dartnall's hypothesis as incorrect? It may be, as he himself suggests, that the derived curve describes not the sensitivity of the light-adapted retina as a whole, but only the sensitivity of a separate brightness-perceiving mechanism playing no part in colour discrimination. This dissociation of luminosity and hue mechanisms is implicit in Granit's dominator-modulator theory of vision. The upper curve of Fig. 1 would then represent the contribution of the colour-perceiving mechanism to the sensitivity of the light-adapted eye. It is interesting to note that this curve does in fact show maxima of sensitivity in those very spectral regions in which Granit has found modulator activity to be most marked, these regions being shown in Fig. 1 by the arrows above the curve.

One merit of Dartnall's hypothesis is, therefore, that it enables an attempt to be made at separating the activity of the brightness mechanism from those of the colour-perceiving mechanisms in the human eye. Unfortunately, because of absence of data, the derived curve cannot at present be continued into the red region of the spectrum.

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IRIDOSCHISIS IN A CASE OF CHRONIC PRIMARY GLAUCOMA*

BY

R. RAMSAY GARDEN *and* A. R. WEAR

BRISTOL

THE term *iridoschisis* was adopted by Loewenstein and Foster (*Brit. J. Ophthal.*, **29**, 277, 1945), for a rare type of iris atrophy of which ten previous cases have so far been recorded. With the exception of two cases aged 46 and 51 years, both regarded as traumatic, all the patients were between the ages of 65 and 94 years.

Shortly after the appearance of the article on a further case of this condition by Loewenstein, Foster and Sledge (*Brit. J. Ophthal.*, **32**, 129, 1948), a patient attended the Bristol Eye Hospital showing to an advanced degree the changes they described. In view of the comparative rarity of the clinical picture, the case, along with a drawing seems worth recording.

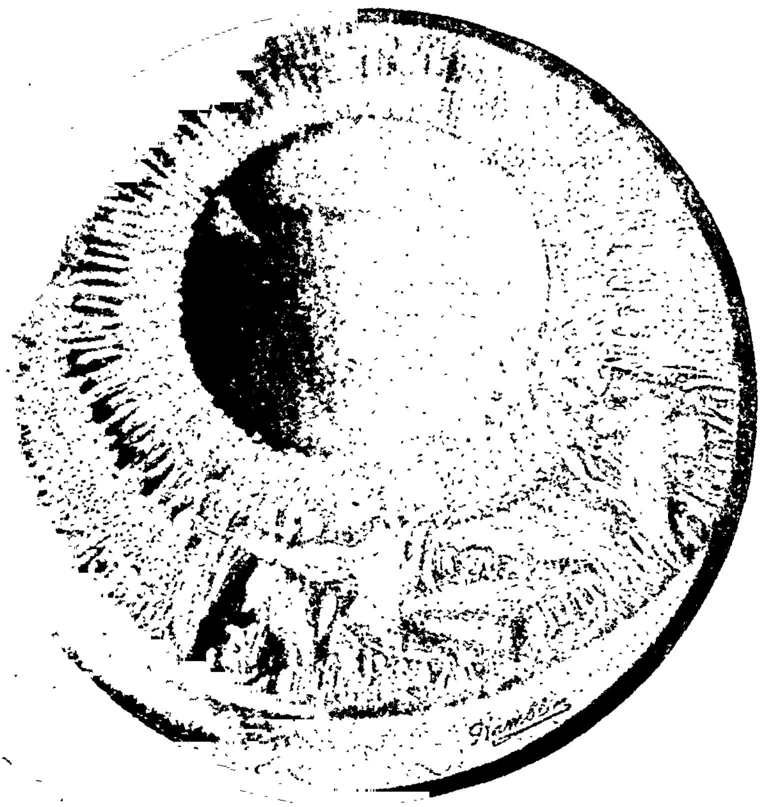

FIG. 1.

* Received for publication, February 14, 1949.

History

The patient, a retired regular soldier, aged 75 years, first attended as an out-patient on March 15, 1944, complaining of failing right vision for some months. At that time he had glaucomatous cupping of the right disc, on which could be seen spontaneous asynchronous arterial and venous pulsation. Corrected vision was R. and L. 6/9; tension R. 100 mm. Hg, L. 36 mm. Hg (Schiötz). Right visual field was markedly contracted and of the glaucomatous type; left visual field was full.

After treatment with pilocarpine drops, the right eye was trephined in the usual way, with peripheral iridectomy, on March 30. The left eye was kept on eserine drops 1 per cent. b.d. and the tension in both eyes remained within normal limits from then onwards, the trephined eye having a rather lower tension for about 12 months.

Although showing no increased intra-ocular pressure, the right eye gradually deteriorated in vision—by July, 1945, to 6/18, and by November, 1946, to 6/60, and there was a gradual reduction of the field almost to the fixation point. Pilocarpine drops 1 per cent. b.d. have been used in this eye since November, 1946.

Clinical picture

On March 5, 1948, it was noted for the first time that the anterior layer of the right iris was atrophied in its lower half, with strands of stroma floating forward into the anterior chamber, having broken off just peripheral to the pupillary border. The ends curled forward and were in some cases adherent to the posterior surface of the cornea. No ectropion of the uvea or visible blood vessels in the strands could be seen; the broken strands and adjacent areas of the stroma were finely peppered with brown pigment. The upper half of the iris, including the peripheral iridectomy, appeared to be unaffected. Tension was normal in each eye, the lenses clear, and the left field full. Vision was R. 1/60, L. 6/9, Wassermann reaction and Kahn were negative.

The suggestion was made that the separation of the iris layers might be due to aqueous seeping down through the iridectomy, but, after the patient had lain on a couch for half-an-hour with the lower end well raised, no change in the iris was noted.

Since March there has been a gradual progression of the condition, and in July large sheets of stroma were found to be detached from the pigment layer, leaving it and the outline of the sphincter pupillae clearly visible; the latter was apparently unaffected by the atrophy. Opacities of the lens are now beginning to appear.

Discussion

The case described belongs to the older age-group in which there was no history of recent trauma to the eye, and would appear to

support Loewenstein and Foster's idea that "the basic change is senile but the process may be aggravated by proteolytic enzymes (lysins) in the aqueous, the product of glaucomatous metabolism." Long-standing glaucoma may lead to iris atrophy and shrinkage of anterior stromal fibres with consequent development of ectropion uveae in many cases. In the case under discussion, however, the pupil has been kept in a state of miosis for fifteen months, and theoretically the taut radial fibres of the iris might rupture as they gradually weakened, instead of producing ectropion uveae. Fixation of the pupil margin by posterior synechiae (as in the first case described by these authors) might conceivably have a similar effect.

The fact that the lower half of the iris is mostly involved in the reported cases of iridoschisis may, as Vogt suggested, be due to gravity, but another possibility is that convection currents in the anterior chamber play a part.

A NOTE ON THE EFFECT OF SLEEP ON GLAUCOMA*

BY

E. M. G. GALTON

LONDON

A DISCUSSION arose in out-patients concerning the effect of sleep on the symptoms associated with a rise in tension in cases under observation for suspected glaucoma. Such varied opinions were put forward and so many different authorities were quoted in support of them, that it was considered worth while to submit the subject to criticism.

A patient who has once had an attack of raised tension, discomfort or even pain in the eye accompanied by blurring of vision during the daytime, or by the appearance of haloes round lights at night, can always recognise a second one as being similar. An attack will often start in the evening when the patient is tired and has settled down to read or sew. She will often volunteer the statement that if she goes to sleep the attack is relieved and she awakes refreshed in the morning.

This clinical observation has been known for many years. Fuchs recorded it in his famous Handbook[1] thus: "When the attacks come on in the evening they always cease with sleep; during the day also, an attack can be interrupted by going to sleep." The point is ignored in most of the modern text-books and the apparent conflict between it and the diurnal variations in the intra-ocular pressure are not discussed.

It is well established that in a normal eye the tension is lowest

* Received for publication, November 16, 1948.

between 1 p.m. and 5 p.m., and that it rises *slightly* (3 mm., Schiötz) during the night to its highest about 5 a.m.[2]. In the early prodromal stage of glaucoma the difference between the lowest and highest readings increases, and the increase occurs much more rapidly. Furthermore, peaks of tension are not confined to the early morning, but may appear at any time during the 24 hrs.[3]. Ultimately the low pressure periods become shorter and shorter until the tension remains up the whole time.

The rise in tension during the night is not fully understood, but is perhaps mainly due to immobility of the lids and eyeball, with consequent lack of massage of the globe by the muscles.

One source of confusion is the well-known fact that in a preglaucomatous eye the tension tends to rise in the dark, due of course to the dilatation of the pupil with blocking of the angle. The Seidel dark-room test is based on this observation. During sleep, however, the pupil contracts, and dilatation from darkness does not occur. It has been suggested that miosis explains the beneficial effect of sleep, and could be looked on as the reverse of the "dark room" effect. In a normal eye dilatation of the pupil in the dark does not raise the intra-ocular pressure[4], because the drainage is so good that filling of the angle makes no difference. Conversely the miosis of sleep does not prevent the normal slight physiological rise. In a pre-glaucomatous eye, however, conditions of drainage are so precariously balanced that the dilatation in the dark causes a rise, whilst the miosis of sleep may, by opening the angle, cause a fall in the tension.

There are other factors to be considered. The anxiety and worry to which this type of patient is so prone is relieved during sleep. In this connection it is interesting to note that a nightmare can precipitate an attack of raised tension. Again, very few people submit to discomfort without taking aspirin or some other analgesic, and this may directly influence the intra-ocular pressure.

The early hours after waking, when a number of adverse factors come into play, are a common time for attacks of cloudy vision and pain. The physiological rise has just passed its peak, and the pupil may be dilated because the patient has been lying in the dark with his eyes open. Prolonged decubitus with no muscular massage to the globe, and the return of psychogenic stimuli may also help to provoke a rise in tension.

I wish to thank Mr. Eugene Wolff for his helpful observations. It was in his clinic at Moorfields Westminster and Central Eye Hospital that the subject was discussed.

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EYE-LASH IN THE LACRIMAL PUNCTUM*

BY

A. J. BOASE

UGANDA

THE arrest of an eye-lash in a lacrimal punctum is said to be a not infrequent occurrence, though many authoritative textbooks do not mention it. Those that do would appear to stress the factor of obstruction. Fuchs specifically alludes to this accident as affecting the *lower* punctum, from which one might infer an immunity for the upper in his experience.

The following case presents unusual features. The patient, a Goan male, aged 50 years, was seen in July, 1944, with an irritating *right* eye. There was marked conjunctival congestion on the nasal side, and between plica and limbus a small phlycten-like nodule which stained with fluorescein. He had had this trouble for 18 days, and was emphatic that the nodule was not there before the eye got red. Treatment with protargol and a lotion had not benefited him. On eversion of the upper lid, the root-end of a lash was seen protruding from the *upper* punctum. It was evident that the lash made contact with the nodule when the eyes converged for near, their normal position throughout his working day as a clerk. The lash was removed and the nodule excised (an innocent granuloma). Healing was uneventful.

The patient returned in January, 1949, this time with his *left* eye inflamed for three days. Conjunctival injection was again limited to the nasal side, and in the middle of it was a small oedematous whitish area which stained with fluorescein. With the previous record before me, I immediately looked at the puncta, and had the satisfaction of removing a lash from the upper one, again with the root end protruding. A rapid cure followed.

The coincidence of this accident happening to both eyes is in itself remarkable, the more so as his puncta do not appear to differ from those of an average person. But of greater interest is the trauma and chronic inflammation which resulted on both occasions from this seemingly trivial mishap. In countless cases of trachoma, wherein short sharp stumpy lashes unceasingly insult the conjunctiva over long periods of time, I have never observed ulceration and granulation as seen in this case. Rather is the expected change one of keratinization. Does this suggest that the rough root of a lash is a more dangerous weapon than its opposite extremity? This theory is supported by another case in my experience where a lash was lodged in the orifice of a central upper meibomian gland with root protruding; it caused more distress than one usually sees with an aberrant lash.

It is to be noted that the factor of lacrimal obstruction did not enter into this case; lacrimation there was, but for obvious reasons of irritation. But should one expect obstruction unless both puncta, or at least the lower one, are obstructed?

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* Received for publication, March 21, 1949

THE SUBCONJUNCTIVAL AB EXTERNO APPROACH IN GLAUCOMA*

BY

EUGENE WOLFF

LONDON

THE *ab externo* approach was described by Gayet in 1884. Since then it has been extensively employed by Czermak, Salzmann, Elschnig, Weekers and others.

I have used the method for the last nine years, at first occasionally, now almost exclusively. The actual procedure was developed in friendly rivalry with Sir Richard Cruise. In the final form of his sclerotomy as described in the British Journal of Ophthalmology for 1947 he used the *ab externo* approach, which I believe he got from me, while I learnt from him the invaluable use of his scleral hook, so that, though there is nothing essentially new in what I am going to say, certain details have been evolved which make the method relatively easy and virtually free from danger of wounding the lens. The operation consists in dissecting down a flap of conjunctiva as for a trephine operation, making an incision with a *scalpel* at the upper limbus, and then doing an iris-inclusion for chronic glaucoma and an iridectomy for acute.

Preparation. The pupil must be small, and well under the influence of a miotic. The usual 4 per cent. cocaine drops at intervals of five minutes are instilled, starting 15 minutes before operation. A small quantity of novocaine, 2 per cent., and adrenalin is injected into the region of the superior rectus and then massaged away through the upper eyelid. If much novocaine is injected, the flap tends later to fall down and makes a stitch necessary. A slightly curved incision is made through the conjunctiva 10 mm. from the limbus, but the operator must take care that the ends are well above the upper limbus. The flap is dissected down to the limbus, but there is no need to split to the cornea. If there is much bleeding a superior rectus suture is put in, and traction made on this: I have found it very effective. A heated probe is only rarely necessary. The next point is the all-important fixation of the eye, for on it depends the ease and safety of the incision. I have tried a great many methods, but have found the following far and away the best. For the right eye I stand behind the patient's head, for the left eye below and to the left side. The patient is asked to look outwards, and a 3 in 4 (or any other favourite) conjunctival forceps placed perpendicularly fixes the internal rectus just to the outer side of the plica.

* Received for publication, March 23, 1949.

The flap is held down with non-toothed forceps by an assistant. With the eye held by the forceps as described above by the left hand, a Cruise's scleral hook is placed on the sclera about 5 mm. from the limbus, the shaft being horizontal. It is pressed backwards very firmly and drawn outwards. A firm hold of the

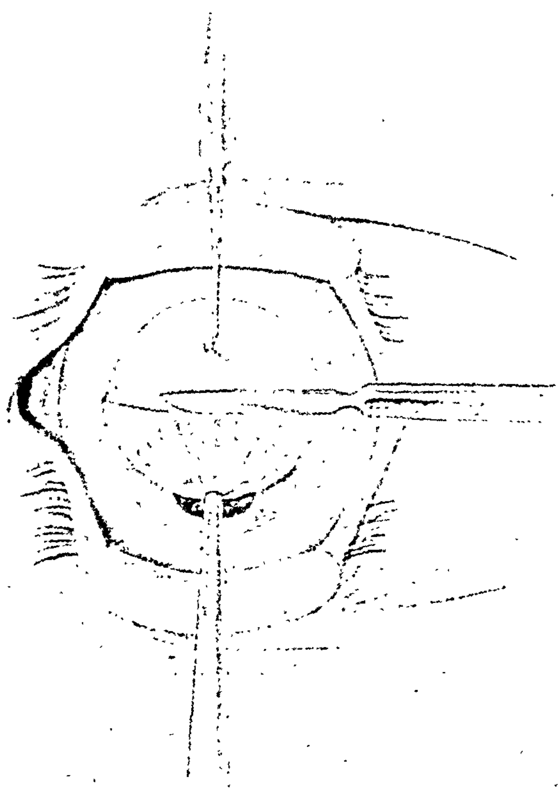

FIG. 1.

sclera will thus be obtained. The eye is now fixed by the hook held in the left hand. With the flap still held down by the assistant a small and exceedingly sharp scalpel is taken in the right hand. With shaft horizontal the blade is placed at right-angles to the upper limbus, and an incision made into the anterior chamber. At first it took me a long time to get through, but with practice it goes much more easily, and often in only a few cuts.

It will be noted that, with the globe fixed in this way, no pressure is made on the ocular contents while the incision is made. As soon as the chamber is entered the iris prolapses. The incision should be about 5 mm. long, and complete through its length. Enlargement of the incision can be done with the scalpel or with fine blunt-pointed scissors.

The actual iris inclusion may be done in many ways, as described by Holth and others. The following is a modification of the Holth Number 2:

The right-hand edge of the prolapse is seized with straight iris forceps, and an incision made into the tent to produce an iridotomy —this goes about half way across the prolapse. The remainder of the iris is pulled into the left-hand edge of the incision and allowed to remain there. The conjunctival flap is now stroked back into position, and usually needs no stitch. In ideal cases there should now be a central pupil with a small peripheral iridectomy, as in a trephine; but the pupil may be drawn up a little, and this is not so good cosmetically, though it does not affect the final result. Atropine is put in, and both eyes tied up. The first dressing is done 24 to 36 hours after the operation. There is usually very little reaction, and the anterior chamber is usually found reformed. A very important point is to start gentle massage straight away. This is done with the thumb pressing through the upper eyelid on the upper edge of the incision. Since I have done this fewer cases have closed up. There is usually very little reaction, and the patients usually leave hospital in from 8 to 10 days. In most cases, after a fortnight or so, a diffuse area of drainage was produced, but sometimes the eye does not drain properly at first, and might even require a miotic for some weeks before it does so.

Comments. I cannot give any statistics, but perhaps it will be more useful if I sum up the advantages and disadvantages of the operation, so far as I see them.

Advantages:

(1) The operation is relatively easy if performed as I have described it.

(2) It is above all a safe operation because,

  (*a*) there is practically no danger of wounding the lens.

  (*b*) the anterior chamber is usually re-formed the day after the operation.

  (*c*) post-operative iritis is rare.

(3) No instrument enters the eye.

(4) A diffuse area of drainage is produced, so that infection is much less likely to occur than with a localised bleb.

Disadvantages.

The great bugbear is the common one of all fistulising operations—namely, that some cases still close up. In the younger group of patients, that is to say below 55 years, there is usually no difficulty in producing drainage, and it is sometimes perhaps too free. But I think that the difficulty increases with age. As I have said before, the number closing up is less, now that one starts massage at the first dressing. It may be suggested that there would be even fewer if the incision were made a little away from the limbus. This is true, but in advanced cases, if this is done the iris does not present, and that makes the operation much more difficult.

My feeling at the moment is that it might be wise to convert the incision into a flap, as Cruise insisted, by a cut upwards at either end.

To sum up: this is a relatively easy, safe method of doing an iris inclusion, with the possibility of enlarging the incision to any desired extent.

The operation for acute glaucoma.

I think it is generally agreed the operation of choice in acute glaucoma is a broad iridectomy, and that the operation with either a Graefe knife or a keratome may be, even in the most expert hands, difficult and dangerous.

The operation *ab externo* for acute glaucoma starts much like that for chronic type except that a retrobulbar injection, 2 cc. of 3 or 4 per cent. novocaine and adrenalin, is given half an hour before. The dissection of the conjunctiva is made as before; the incision may be placed 1 mm. above the upper limbus, and the iris prolapses. The right-hand edge of the prolapse is seized with iris forceps and drawn over to the left, and a radial incision made with de Wecker's scissors so as to include the pupil. The iris is pulled further over to the left, as in the classical operation, to tear it from its attachment to the ciliary body, and then over to the right, and cut off.

The great advantage of doing the iridectomy by this method is its safety, for obviously it does not matter how shallow the anterior chamber is. The simplicity of the method may be judged from the fact that house surgeons do it quite well at the first attempt.

The only disadvantage, if so it may be called, is that not infrequently a draining area is produced, as after the iris-inclusion operation. This is probably due to the fact that it is difficult to replace the iris at the edges of the incision.

There is one last thing, and that is a consideration of the simplicity of the instruments used. The perfect Graefe knife and

really sharp keratome are only found among the instruments of the ophthalmic surgeon or eye hospital. The operations described above can be done with instruments in everyday use—scalpel and scissors are easy to come by. The hook, although exceedingly useful, can be replaced by a stitch, or the incision can be done with fixation on the internal rectus. Also the work of the de Weckers can be done with ordinary scissors.

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ON THE USE OF AMNIOTIC MEMBRANE

BY

C. DANSEY-BROWNING

LONDON

CAPTAIN C., aged 30 years. The benign melanoma conjunctivae situated at the external canthus of the left eye, had recently shown signs of extension. Fig. 1, August 19, 1948. The growth was

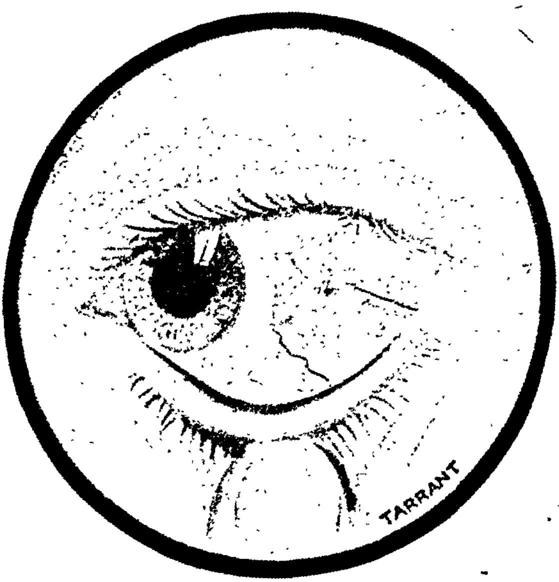

FIG. 1.

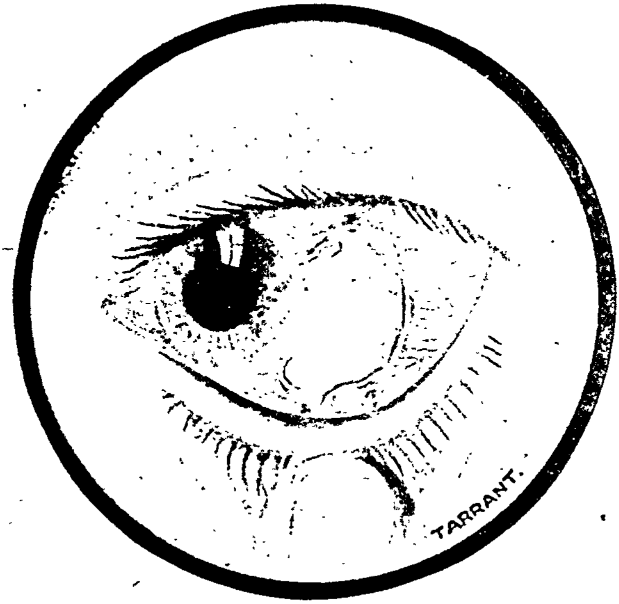

Fig. 2.

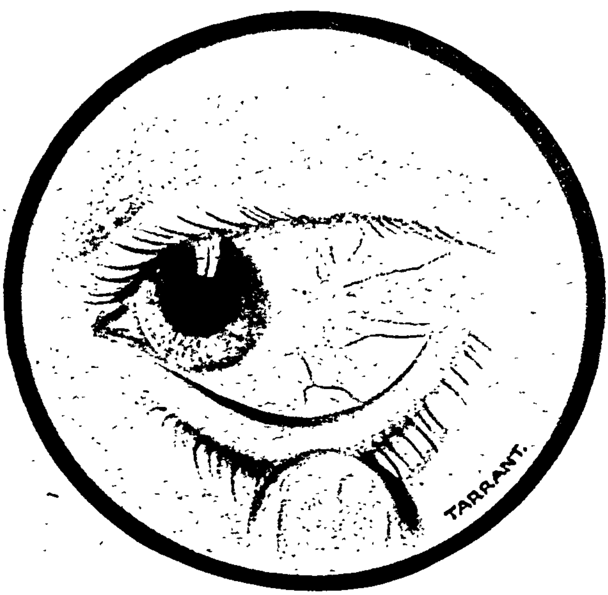

Fig. 3.

excised on August 20, 1948, and a piece of London Hospital sterile amniotic membrane (Morley's process—fat-free) of the same size as the raw area, was sutured into position.

The appearance of the eye some four days after the operation is shown in Fig. 2, August 24, 1948, The appearance of the conjunctiva a month after operation is shown in Fig. 3, September 29, 1948.

It is felt that these representations of the appearance of the eye during the regeneration period of the conjunctiva are of interest. Also they indicate a possible use for amniotic membrane in the early treatment of ophthalmic wounds in war-time, particularly in the mobile ophthalmic units in forward areas.

UNUSUAL OCULAR FOREIGN BODY

BY

NIRMAL KUMAR GHOSE

CALCUTTA

VARIOUS authors have reported the occurrence of different types of intra-ocular worms, but the occurrence of a snail in the eye must be of extreme rarity, if indeed it has ever been known.

Case Report

K.R M., a 16-year old male, came on October 1, 1948, with a history of irritability in the left eye together with deep left orbital aching of one week's duration. These symptoms began about half an-hour after washing his face in a pond.

Examination revealed superficial punctate keratitis and the inferior palpebral conjunctiva was congested There were large follicles in rows upon the lower fornix. While the lower fornix was being examined a small snail emerged apex first from under the conjunctiva, and started moving across the palpebral conjunctiva. It was picked up by a swab-stick, and preserved in formalin.

On more detailed examination corneal sensation was found lost and the pre-auricular gland enlarged. Slit-lamp examination showed typical sub-epithelial infiltration and blebs.

The deep boring pain passed away about two minutes after the emergence of the snail. The keratitis cleared up completely with dark glasses, normal saline, Ung. Atropine 1 per cent., and Sterodin—2 c.c. every other day, and by October 12, 1948, he was cured.

The snail was taken to the Department of Helminthology in the School of Tropical Medicine, and was identified as a young *Vivipara Bengalensis*,

The size of the snail is vertically apex to base one mm., and horizontally 2 mm. I was told that a week earlier the size would have been no larger than a grain of sand.

Discussion

How did such an unusual foreign body go under the conjunctiva? These organisms do not have teeth, and they do not burrow. Probably the patient, feeling the gritty sensation of a foreign body in the eye, gave a good rub, and the snail's sharp shell-apex punctured the conjunctiva and went under it.

I was also informed that it can easily survive in such sheltered conditions, but rapidly dies on exposure to air. Whether the associated corneal condition was fortuitous or a complication is uncertain, but we were seeing a few K.P.S. cases every day at that period, so it may have been a coincidence.

My thanks are due to Dr. A. K. Mukherjee and Dr. N. Bhaduri, Department of Helminthology, School of Tropical Medicine, for valuable aid and advice, and to Dr. A. C. Ukil, Superintendent, Medical College Hospitals, Calcutta, for permission to publish this case.

OBITUARY

PROFESSOR V. ROSSI

VINCENZO ROSSI qualified as a medical man at Naples University in 1914, and became an assistant at the ophthalmic clinic of that university in the following year. Here he worked for a number of years under the late Professor Angelucci. In 1929 he was appointed Professor of Ophthalmology at the University of Modena, and afterwards at Pisa University. His academic output covered a wide range of subjects, including trachoma, endocrinology and glaucoma, but perhaps his chief interest lay in linking-up ophthalmic signs with general derangement of the constitution. His first and only visit to England was made in April this year, when he attended the annual Congress of the Ophthalmological Society of the United Kingdom, but long before that time his work and reputation had become familiar to readers all over the world. The news of his sudden death towards the end of June was distressing, because Professor Rossi was a courteous and accomplished gentleman, typical of Latin civilisation at its best. He will be greatly missed at the International Congress which he had looked forward to attending in 1950. Readers will deeply sympathise with the members of his family circle in their heavy loss.

BOOK NOTICE

The Practice of Refraction. By SIR STEWART DUKE-ELDER. J. & A. Churchill, Ltd., 1949. Price 18/-.

This is the fifth edition of what is obviously a very popular work on Refraction. Its popularity is due to clear exposition of what is really a complicated subject, and most students will be relieved at the total absence of mathematical formulae. It was a bold move to exclude such formulae, but the explanations given are sufficiently clear to be comprehended by the average reader.

The improvements in this new edition are many, and among these the discussion on myopia deserves special commendation. It places myopia in its proper setting as a biological variation, and under the heading of "visual hygiene" does away with the fear which its presence engenders. Thus many a child will be spared drastic curtailment of his education and under-correction of his error. The idea that close work causes or aggravates myopia dies hard.

The treatment of streak retinoscopy and velonoskiascopy and aniseikonia is adequate.

One misprint has been noted on p. 285 — LEISS for ZEISS. It is difficult to understand a sentence on page 76, where it is stated that the corneal radius varies from 7 to 8.5 mm. "A variation which involves a refractive difference of two-thirds of a dioptre," whereas the correct figure is given on page 64, 1 mm. = 6D. Nor in the opinion of the reviewer is increased corneal curvature such an exceedingly rare cause of myopia.

On the subject of trifocal lenses on p. 249 it is better from the manufacturers' point of view that the intermediate portion should be half the total near addition. In the example given distance + 1.0, intermediate + 2.5, near + 4.0 would be better than + 1.0, + 3.0, + 4.0 as stated.

In multifocal lenses it might have been pointed out that, while the continuously variable curve is moderately satisfactory in the vertical central line of the lens, the distortion on either side of this line is too great for comfort. In dealing with high-power lenses no mention is made of the use of aspherical lenses for cataract cases, as in the form of the catral lens of Zeiss, or the deep curve English-made lens — the Rotoid.

These all are minor blemishes as is also the occasional use of awkward words such as "disabilitating" on page 289, and the use of the term "ophthalmological lenses" instead of "ophthalmic lenses." It only remains to add that throughout the book is well printed, the drawing clear and well designed. The student of refraction will be well advised to read and study this book.

CASE NOTE

BY

F. W. G. SMITH

WESTGATE-ON-SEA

I do not think the use of an Amsler's needle for the treatment of implantation cysts of the anterior chamber has been mentioned in ophthalmic literature.

A boy, aged twelve years, received a perforating injury of the left eye with a pointed stick in January, 1947. The case was seen by Mr. T. M. O'Neill and myself. The prolapsed iris was excised and a thin piece of wood, 10×2 mm., removed from the interior of the eye at the same time. The eye settled down without causing anxiety.

In May, 1949, the eye became slightly inflamed, and a cyst, 4×3 mm., was seen in the anterior chamber. The base was attached to a scar at 9 o'clock on the limbus, where the original injury had occurred. The slit-lamp showed endothelial bedewing and a slight flare; but no K.P.

Under general anaesthesia the cyst was evacuated by an Amsler's needle on a small syringe, passed through the attached base and refilled with pure carbolic acid which was sucked out, after a couple of seconds, as soon as the cyst wall became white and opaque.

The eye settled down rapidly, and a small amount of white fibrous tissue was all that remained of the cyst when the case was seen recently.

NOTES

IN accordance with the wishes expressed by many readers, medico-political questions will as far as possible be excluded from future numbers of the Journal. The Editorial Board does not seek to belittle the importance of such questions, because every practising ophthalmologist, whether he knows it or not, is closely concerned with medico-political matters. Nevertheless it seems more than ever desirable for the Journal to be clinical and academic in its policy. Admittedly some questions are on the borderline between academic and medico-political territory, and such a line is not always sharply defined, but the Editorial Board will strive to make equitable decisions in all doubtful instances.

It has recently been the custom to publish the gist of the proceedings at Council Meetings of the Faculty of Ophthalmologists. That practice will now be abandoned, partly because the inclusion of such matter has encouraged other bodies with a more pronounced political flavour to seek publicity in the Journal. The Council of the Faculty wishes to announce, however, that the *British Medical Journal* and the *Lancet* will continue to be furnished with a resumé of the decisions and recommendations made at Council Meetings.

* * * *

SIR STEWART DUKE-ELDER has been elected an Honorary Member of the Swedish and Danish Ophthalmological Societies.

Presentation

THE Katherine Bishop Harman prize was presented to Dr. Charles Swan at the June-July meeting of the British Medical Association.

* * * *

Corneo-Plastic Unit and Eye Bank

THE South Eastern Metropolitan Regional Hospital Board has approved the establishment of a corneo-plastic unit and eye bank in connection with the plastic centre at East Grinstead. This unit deals especially with cases of corneal graft and the eye complications of maxillo-facial trauma, such as cantho-rhinostomies, socket and orbit reconstructions, paralysis of extra-ocular muscles, ptosis and the various types of enucleation implants, etc. Beds have been set aside for the purpose, and a Marks' Scholarship has been allocated for clinical research in these subjects. Demonstrations and courses of instruction will be arranged from time to time.

The eye bank is additional to the existing cartilage bank. Special facilities such as superficial X-ray therapy for corneal graft cases are available, and a photographic unit provides serial records in every case.

* * * *

Ophthalmological Society of Egypt

IN order to encourage scientific ophthalmic work, the Ophthalmological Society of Egypt has decided to grant a prize, to the value of 20 Egyptian pounds, for the most valuable contribution brought up before the Annual Congress of the Society. These should be in the hands of the judges not later than December 1, 1949.

Papers submitted for publication should be sent to :—

The Secretary of the Editorial Committee,

British Journal of Ophthalmology,

Institute of Ophthalmology, Judd Street, London, W.C.1

Papers should be accompanied by a statement that they have not already been published elsewhere, and that they will not subsequently be offered to another publisher without consent of the B.J.O. Editorial Board.

All papers must be typewritten in double spacing on one side of the paper only, with a blank margin of $1\frac{1}{2}$ inch. The Author's name and address should be plainly indicated. Illustrations should be detachable from the typescript, and numbered in sequence; and the upper edge of each should be marked "TOP" for the printer's guidance. Each illustration should be marked on the back with the author's name. References to the literature should be listed with the authors' names alphabetically arranged, and set out in the Harvard system, *e.g.*, LANGLEY, J. N. (1919). *J. Physiol.*, **53**, 120. Information concerning reprinted copies will be despatched with galley-proofs to the authors of articles accepted for publication.

// THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

SEPTEMBER, 1949

COMMUNICATIONS

SOME ASPECTS OF OCULAR MELANOTIC GROWTH*

BY

ARNOLD LOEWENSTEIN

GLASGOW

FROM THE TENNENT INSTITUTE OF OPHTHALMOLOGY
UNIVERSITY OF GLASGOW (PROF W. J. B. RIDDELL)

IDA MANN (1926) stressed some years ago her conviction that the question of pigment origin must not be looked upon from the narrow sphere of ophthalmological pathology. Jean Nordmann (1947), indeed, has subscribed to this demand in an admirable way, so far as could be achieved in a short survey attempting to follow up the origin of the pigmented cells in the higher vertebrates. Relationship to light is one aspect, the influence of the hypothalamus another; such views are plentiful. Restriction to higher vertebrates appears to be dictated by sheer necessity.

Even the narrow ophthalmological outlook, however, offers a *tremendous mass of unsolved puzzles involving embryology.*

Dedicated to Professor J. Meller.

* Received for publication, August 19, 1948.

anatomy, physiology and, especially, pathology. The ophthalmologist's interest is certainly not limited to theoretical considerations as the growth of pigmented tumours engages our clinical interest so frequently. Basic difference of opinion is rife in the assessment of many pigmented growths, not only with regard to origin, but also to clinical behaviour and, last but not least, to treatment. Investigation of new material, especially if examined with varying technique, appears indicated in spite of the presence of a considerable literature covering this subject.

It is pigment production, the deposition of melanin, or one of the melanin substances, in these blastomata which dominates our attitude towards them. A non-pigmented wart growing at the lid margin would hardly worry us, while a pigmented new growth is the object of our justified concern.

Ribbert's conception (1911) of the mesodermic origin of the pigmented uveal growth remained unchallenged for years, and the malignant choroidal melanoma, the chromatophoroma, was considered as a melanosarcoma. This was hardly changed when T. W. Dawson (1925) and his Edinburgh school (E. K. Dawson, Innes and Harvey, 1939) tried hard to prove that these melanotic blastomata are ectodermal, and derive from the retinal pigment epithelium. Single cases of bulbus-filling melanotic masses of epithelial character have been described by Schuster (1918) and Pascheff (1929). Both assume an origin of the growth in the hexagonal layer. In recent years the name melanosarcoma—although still used clinically—is more and more abandoned in favour of the less committal "malignant uveal melanoma" as the shape of the tumour cells does not correspond frequently to the sarcoma type. Levkojeva (1940) found out of 202 malignant uveal blastomata only a small group which she considered as sarcoma type. We stress, however, here the fallacy of a decision reached from examination of routine sections, unless supplemented by flat sections or bulk examination of the cleared specimen.

A great change in the conception of pigmented growths came with Masson's papers (1926) which went back to Verocay's publication (1910). Verocay had shown that the neuro-fibromatous tumours in von Recklinghausen's disease were outgrowths from Schwann's sheath. Masson's revolutionizing work was concerned with the cutaneous naevus which he assumed to be a neural tumour, a Schwannoma. Schwann's cells are the melanin producing units, the melanoblasts. G. Dvorak-Theobald (1937) took up Masson's new idea and showed, investigating 6 malignant choroidal melanomata, that in 5 of them a tumour growth might have started in the long posterior ciliary nerves. Her paper influenced the English-speaking ophthalmological world in favour of Masson's theory.

She quoted Berger and Vaillantcourt (1934), who had already assumed that ocular melanomata are derivates from Schwann's cells. Nordmann (p. 116) is sure that uveal tissue generally is not simply mesodermal. Its mass of nerve fibres and nerve cells are closely interwoven with the pigment network. The malignant uveal blastoma is a special type of new growth in which choroidal melanophores and glial cells are a product of selective disintegration of Schwann's sheaths.

General pathologists and ophthalmologists were soon ready to accept the neuro-ectodermal theory of the origin of the naevus growth and consequently of the malignant uveal melanomata which were considered generally as neuro-ectodermal with no exception. Dawson's ectodermal theory was hardly mentioned in ophthalmological literature.

Eugene Wolff in his W. Mackenzie Memorial lecture (Glasgow, October 24, 1947) challenged the general validity of Masson's theory and added new material against it in a paper read at the meeting of the Ophthalmological Society, London, April 8, 1948. According to Wolff the naevus is regarded as a composite or mixed tumour consisting of naevus cells, epithelial cells and branched chromatophores. Each of these cell types may proliferate alone or with others and produce a malignant pigmented tumour. The final structure depends on the relative proportion of the three types of cells.

Wolff's lecture stimulated a revision of material which I had collected over some years, the pigmented benign naevi at the lid margin and limbus and the malignant pigmented types of these regions, the naevi from the iris and choroid and finally the frequent iridic and choroidal malignant melanomata. It will be understood that certain aspects only will be discussed, seen from the *point of view of classification, pathogenesis, propagation, etc.*

The first type of melanotic growth which deserves special attention is the so-called naevus cysticus. There was a dark patch on the left eye at the limbal conjunctiva of a 16-year-old boy which was observed growing during a few weeks. Prof. A. J. Ballantyne, to whom I am indebted for the specimen, excised the growth, which could be peeled off easily from the sclera. It started growing again after two years. The tumour consists of normal conjunctival tissue with many goblet cells. There are (Fig. 1, A and B) densely packed, mostly round, dark-stained naevus cells with hardly any plasm. There is no typical gland formation, but great numbers of cystic spaces, mostly empty, some containing a fibrinous substance. Mucicarmin staining shows many goblet cells filled with mucin, and mucin is proven to be within the cystic spaces. Epithelial bridges link the conjunctival epithelium with

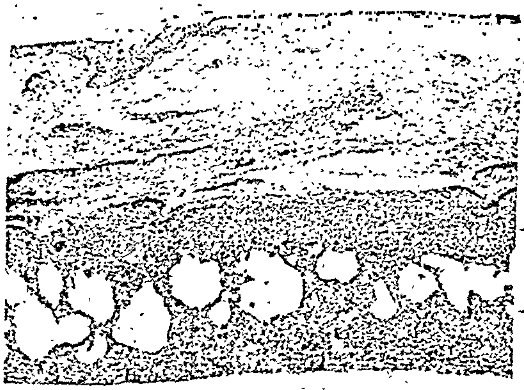

FIG. 1.

Naevus cysticus (M), at limbus area. H.E. 150 ×
Naevus cells with many mucous patches (goblet cells).

FIG. 1A.

FIG. 1B.

Naevus pigmentosus cysticus. Mucicarmin staining. Note the (carmin red) swollen mucin containing naevus cells. 300 ×.

the naevus-cell tumour. There is a moderate pigmented content, best visible in unstained specimens. Cuenod and Nataf (1934) have shown several conjunctival cystic naevi in slit-lamp pictures.

The naevus nature of this growth is beyond doubt. So is the mucin production of its cells. The goblet cells within the tumour cannot be distinguished from those of the bulbar conjunctiva. The linkage between the conjunctival epithelium and the naevus growth is obvious. We do not doubt, therefore, that this type of cystic naevus appears to be derived from the epithelium as Unna (1893), Dawson (1925) and many others have assumed for the naevus generally.

There is another pigmented growth to be discussed which grew at the lid margin and appeared clinically as a pigmented rodent ulcer. It was excised in the whole thickness and the defect closed with a Buedinger-Mueller—whole thickness—auricle-flap (J. Foster). Histological investigation showed a naevus cell growth of unusual size which invaded (Fig. 2, A, B, C) the area of skin, Meibomian glands and palpebral conjunctiva. The epithelium of the skin as well as that of the conjunctiva has sent out downgrowths of considerable depth of a controlled cell type. The majority of the naevus cells are typical, small, dark, without cytoplasm, and with a moderate pigment content. Some of the islets

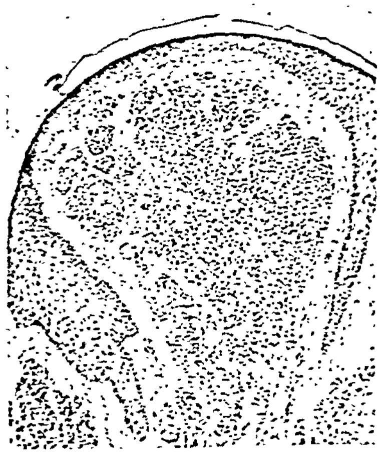

FIG. 2A.

Naevus pigmentosus of lower lid margin. H.E. 150×. Note thinning of epithelial cover over naevus growth and down growth of the skin epithelium at both sides of the naevus.

consist of larger cells with a clear plasm (Fig. 2, B) which have real epithelial character. Mucin reaction was negative everywhere except in the epithelial downgrowths of the conjunctiva.

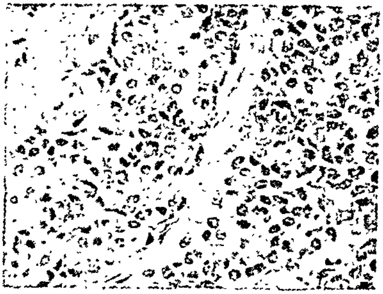

FIG. 2B.

Pigmented naevus at lower lid margin, H.E. 450×. Note the clear epithelial naevus islets to the left while the remaining naevus cells are dark with very little plasm.

FIG. 2C.

Naevus pigmentosus of lower lid margin. H.E. 60×. The benign-looking naevus cells infiltrate the sebaceous glands. Note the downgrowth of the *conjunctival* epithelium.

The presence of both naevus cell types, the small, dark one with no cellular plasm, and the epithelial type side by side, is one point of interest. The other is the new growth of skin and conjunctiva which had created clinically the impression of a pigmented rodent ulcer. Our conception of this case is a primary growth of the

naevus cell explantate resting at the lid margin, probably since birth or earlier. It started growing at a certain age. We feel that this naevus cell growth is the stimulus for both types of *epithelial* outgrowth in conjunctiva and skin. Products of the naevus cell metabolism might work as growth promoting factors, as do the large groups of carcinogenous compounds. The "Melanins" are different chemically from all so far known carcinogenous substances.

Wolff's conception of the naevus as a mixed group of cells, typical naevus and epithelial cells, here seems to receive confirmation. Even branched chromatophores were present in small

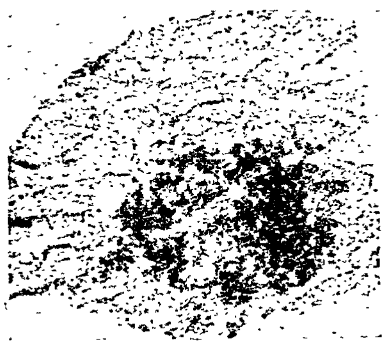

FIG. 3.

Choroidal naevus discovered by chance in flat choroid unstained seen from scleral side. 60 × approx.

numbers, which might originate in the cells of Langerhans (Pascheff, 1946).

Choroidal naevi are certainly more frequent than we assume or than the scanty literature suggests. There is practically no possibility of a differential diagnosis between a beginning malignant melanoma and an innocent naevus, clinically. Such a diagnosis is frequently not even anatomically secured, as we shall show. Ophthalmoscopic control with repeated fundus photography seems to be the only way to discover the first sign of growth.

We were able to demonstrate two choroidal naevi anatomically, both found by chance in fixed, opened eyes, by routine slit-lamp examination. In neither case was a new growth, pigmented or unpigmented, present.

In the first case the dark choroidal patch was excised with a 4 mm. trephine, cleared in glycerine and photographed unstained (Fig. 3). Then the piece of choroid was embedded in paraffin,

cut and stained; depigmented slides showed the cell structure considerably better (Fig. 4).

The cell type is a spindle-cell form, denser in the outer choroidal layer, where pigmentation is heavier. The nuclei are of great inequality; although most of them are slim, they range from 2 to 15 μ in length, and from 2 to 5 μ in cross diameter. The pigment is in fine granules, round, resembling cocci of less than 1 μ diameter; where it is packed in branched melanophores it appears darker brown, but the size of the granules is still the same. The distinction from the rod-like retinal pigment in the same microscopic field is obvious. Some of the bigger "chromatophores" have no branches left. They are huge round cells packed with brown granules. Here we discover larger pigmented granules, which are caused, obviously, by fusion of the small equal granules. We have, therefore, to call the cells with the small

FIG. 4.

Choroidal naevus, depigmented. H.E. 300×.

brown granules of equal size melanoblasts, according to D. T. Smith (1925), while the bigger, heavier pigmented cells containing pigment granules of different size are chromatophores. The first produce the pigment granules, the latter store them.

The majority of these cells do not resemble a naevus-cell growth. They are mostly longer and spindle-shaped, that being the reason why older authors protested against the name choroidal naevus. Some cell groups of our two cases consist of small dark stained cells without cytoplasm, and are reminiscent of naevus cells of the skin. But we must not lay too much stress on the morphology of the cell type, generally. The great polymorphism of the melanoma cells is quite evident from the 14 different types of this blastoma distinguished in the classical work of Ernst Fuchs (1882). Even the retinoblastoma with its foetal, small, dark, round nuclei shows spindle-shaped cells in cases where the tumour has perforated the bulbar coats and grows in the soft orbital tissue.

This, indeed, was so striking that early authors spoke of a transformation of glioma to sarcoma. The tissue pressure undoubtedly exerts great influence upon the shape of the growing cells.

The choriocapillaris is nearly everywhere well preserved and Bruch's membrane intact. In our second case the structure of the growth is denser, the spindle cells are close together, the nuclei mostly dark stained, the pigment forms clumps, its granules are of different size, "melanoblasts" are absent. Branched chromatophores in the sclera are numerous, especially surrounding the pigmented ciliary nerve which joins the choroid in the naevus

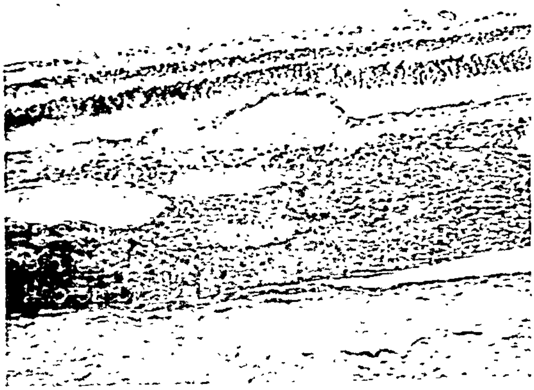

FIG. 5.

Choroidal naevus 2. H.E. 300×. Note: subretinal exudate over naevus.

area. While the greater part of the naevus leaves the choriocapillaris intact, there is a region where the naevus growth reaches Bruch's membrane and interferes with the choriocapillaris. Here a granular substance with eosin red shadows and empty vacuoles lifts the hexagonal cells (Fig. 5). It looks like an exudate between the intact Bruch's membrane and pigment epithelium. There is little doubt that this exudate is caused by the choroidal change, which here reaches its greatest intensity.

We have observed retinal disintegration frequently over choroidal malignant melanomata, even over small tumours (Fig. 6). It is interesting to note that this regressive process is present directly over the new growth and not over subretinal fluid often found adjacent to the tumour. This cystic degeneration of retinal tissue situated over a choroidal melanoma might be used diagnostically for tumour identification, as we have seen lately. We conclude that retinal nutrition might suffer when the vascular tissue

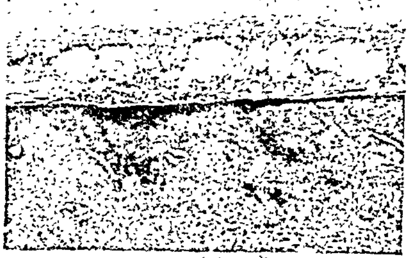

FIG. 6.

Malignant choroidal melanoma. H.E. 60× approx. Note cystic retinal degeneration over the tumour area exclusively. Not present over the serous detachment without tumour infiltration.

of the choroidal sponge is partly replaced by tumour growth. It seems interesting that a disturbance of such small size could be observed in a non-malignant growth of naevus character.

Anatomical investigation of these two choroidal naevi does not permit conclusive opinion as to the origin of these pigmented cells. At any rate, melanophores are present besides melanoblasts and the cells resemble a neurofibroma. We assume cell rests possibly of Schwannoma character, but we would not exclude displaced cells of the outer layer of the secondary eye vesicle.

We discuss a case of flat small malignant melanoma of mixed cell type with moderate histological malignancy and fatty necrosis. The small tumour was linked with the posterior ciliary nerve. The same cell type was present in the tumour tissue infiltrating the ciliary nerve. The branched chromatophores in the nerve tissue were especially well developed. Branched chromatophores were present in the sclera as well. Here we might assume the melanotic growth to have arisen from Schwann's sheath of the ciliary nerve. But it might be the other way; the malignant melanoma might have grown out from the choroidal tumour through the scleral emissarium following the line of least resistance. We are inclined to this conception, especially in a case of a more developed malignant melanoma in which huge contracted melanophores are amassed in the choroidal tumour and in the pigmented infiltrate of the ciliary nerve. The old conception of growth through the emissarium appeals especially in a case of big malignant melanoma which grew through the whole scleral thickness and ended in a black knob of about $\frac{3}{4}$ mm. diameter.

Loewenstein (1945) has described an interesting pigmented growth of the disc. This eye showed with other features a heavily

pigmented ciliary nerve entering the choroid where this tissue is thickened to twice its normal thickness. Nearly the whole choroidal tissue is formed by branched chromatophores. Between the dark pigmented chromatophores slim parallel arranged nuclei are visible of the same shape and size as the nuclei of Schwann's sheath in the adjacent posterior ciliary nerve. Loewenstein has explained the pigmented disc tumour as misplaced cells of the outer layer of the secondary eye vesicle, primitive cells, cell rests in the sense of Cohnheim, a phakoma with the inherent power of pigment production. Something similar might have happened in the same eye in the choroid where cell rests have produced a tissue belonging to the choroidal naevus group.

Summarizing our conception about choroidal naevi we assume *the existence of cell rests possibly developmentally displaced.* Schwann's cells might be the origin. The possibility that the outer layer of the secondary eye vesicle might be the source must be fully acknowledged. Both sources have the power of forming pigment. There is no reason to put the origin of malignant melanomata on another footing from the benign ones. Both types start in the outer layers of the choroid.

Wolff has found typical chromatophores in pigmented naevi of the conjunctiva. He identifies them with the mesodermal chromatophores (melanoblasts). We have seen similar structures in a malignant degenerated pigmented naevus at the limbus in flat sections and razor slides. We know fibroblasts of the conjunctiva have a great phagocytic power. The same is true of the cells of preretinal tissue. Seen in flat specimens these fibroblasts are branching and the tentacles are full of fat granules and pigmented corpuscles. They resemble, indeed, the choroidal chromatophores, especially those of the superficial layers. If we spread a choroid from a case of old chronic uveitis and stain it for fat with scarlet red the dendritic chromatophores are full of shining red fatty globules of different size and light brown pigment granules. We assume that these chromatophores have taken up pigment granules produced by the melanoblasts. The phagocytic power of these chromatophores is not exhausted by the absorption of pigment debris as they are able to absorb fatty droplets in addition. These cells belong, in our opinion, to the reticulo-endothelial system, which forms another group of melanotic growth.

Loewenstein (1930) has seen a man of 41 years of fair complexion with no other clinical signs of a melanotic tumour. Small blackish nodules were discovered in the conjunctiva of all four of his lids. These nodules varied in size from 0·2 to 2·0 mm., they were mostly round or nearly so, one had a morular form. The conjunctival vessels surrounding the nodule were definitely

dilated. The colour of the pigmented nodules was not homogeneous, some were dark coffee brown, others light brown and some had a slight greenish hue.

The patient had used a collyrium once or twice daily for about ten years. It contained, besides zinc sulphate, adrenalin. No biopsy was possible. Animal experiment (rabbits) were performed. A collyrium with adrenalin was applied twice daily for a year without result. Subconjunctival injection for 18 months twice weekly approx., however, produced besides an increase in physiological epithelial pigment at the limbus, a group of blackish

FIG. 7A.

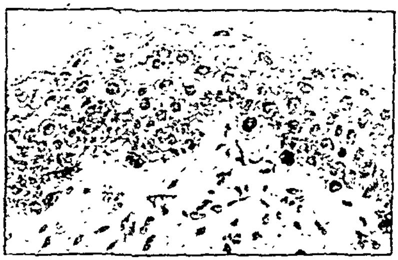

FIG. 7B.

nodules, similar, indeed, to those seen in the patient. Histologically (Fig. 7, A and B), there were melanin granules within the conjunctival epithelium, especially within the basal cells. Besides this epithelial pigment, there were many huge round or polyhedric reticulum cells filled with melanin granules.

The relationship of adrenalin and melanin is well established (Neuberg 1908). We know that homogentisinic acid is a product similar to adrenalin, and is the basic substance in alkaptonuria and ochronosis (deposits of melanin in many tissues). Naevus-like conjunctival pigmentation was shown by *Cuenod and Nataf* (1934) in a case of alkaptonuric ochronosis.

Similar melanotic changes in the conjunctiva have been described by Velhagen (1931) among workers in hydroquinone, a

substance belonging to the adrenalin group as well. Banks Anderson (1947) has published kodachromes of these melanotic changes in the conjunctiva, cornea and sclera in this industrial disease. Anderson's histological findings in biopsies are very similar to our own in the rabbit. He did not succeed in producing the changes in the animal experiment (continuation of the experiment was not long enough). Some lesions in the workers investigated by Anderson resembled the precancerous Bowen's disease, an observation which deserves careful consideration.

Describing precancerous melanosis Reese (1943) mentions varying numbers of cells in the submucosa, containing phagocytosed pigment. This might, according to Reese, originate in the basal epithelial layers. The exact mode of malignant transformation is not known. It seems to be the activity of basal epithelial layers from where the malignant proliferation spreads.

Observation of the adrenalin melanomata of the patient and of the rabbit has proved that adrenalin and its pigmented derivates are reabsorbed by the cells of the reticulo-endothelial system and stored. The same procedure seems to occur with hydroquinone workers. These little tumours are pigmented reticulo-endotheliomata. Future investigation may show whether they are the first stage of a malignant development or not.

The nature of the pigmented granules within the melanophores (or melanoblasts) is, unfortunately, completely obscure. Have they an independent life, reproducing by division, or are they a secreted end-product? It is of the same great interest whether, in the case of malignant melanoma, the pigment granules represent the tumour elements or only the innocent result of cellular disintegration. As far as is known this important problem is still unsolved. Pigment infiltration in the trabecular area and in the wall of the collector veins was demonstrated at Oxford in 1948.

We have investigated in a case of malignant melanoma of the iris and ciliary body the paths of elimination, from the anterior chamber. In one part of the specimen routine sections were performed. They showed (Fig. 8) the pigment growth in iris and ciliary body. The trabeculum is filled with a blackish mass. Schlemm's canal and collector veins are embedded in blackish granules. With oil immersion we can study the granules in the scleral part of a collector vessel. There are no cells visible, but granules of different size distributed in the wall of these "aqueous" veins (Ascher) in varying density. We get the impression that the pigmented detritus from the uveal melanoma suspended in the aqueous floated with the aqueous movement into the collector vessels. Many of these pigmented granules are taken up by reticulum cells.

FIG. 8.

W., female. Malignant melanoma of iris root and ciliary body. H.E. 60×. The dark infiltration of the circulus venosus is restricted to the area of the uveal melanoma.

Mayou (1930) has shown a similar appearance in his first case, in which the area of Schlemm's canal was infiltrated with pigment. He attributes importance to this involvement since in his opinion it might be the only means of distinguishing an innocent from a malignant growth. Gonioscopic investigation of these cases appears indicated.

This type of distribution of the melanoma débris was even more evident with another kind of preparation. In the remaining tissue of the excised eye the uvea was removed by a cyclodialysis from the sclera and the anterior part, cornea and sclera, was cleared with wintergreen oil and studied unstained. Here the blackish infiltration of the drainage area is evident (Fig. 9). With

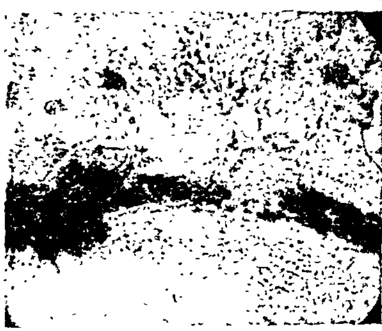

FIG. 9.

W.f. malignant melanoma of iris root and ciliary body. Hem. Cleared sclera and cornea. 60×. Seen from ant. chamber. Tumour infiltrated areas of trabecular network restricted to uveal tumour area. Pigment.

high power we recognise that the pigmentary granules are present along the aqueous veins (Ascher), but no cellular structures are visible. Although no metastatic cells are found the impression of a propagation of the melanoma along the drainage system is strong. This kind of pigment infiltration is different from the common one we find in cases of iridocyclitis, glaucoma or even in healthy eyes of elderly people. Here, the specimen is prepared in a similar way, the pigment in the endothelial cells of the trabeculum fibres is dirty-brown, of irregular shape, the product of wear and tear of the uveal tissue. We think that the pigmentary elements found in the anterior drainage system of the case of malignant melanoma in the anterior uvea might contain the living tumour granules. No definite decision is possible if based on anatomical findings exclusively.

The propagation of a choroidal malignant melanoma is even more complicated if we consider the reaction of the hexagonal cells. The pigmented cells of the retinal layer start growing into retinal tissue under varied conditions, so that pigment cells found in the retina in cases of malignant choroidal melanoma cannot be reasonably regarded as tumour cells.

We peeled off parts of the retina from several malignant choroidal melanomata, stained the pieces in bulk, cleared the tissue and studied the situation in the flat specimen. Retina can be separated from the tumour with difficulty only, but we succeeded at some places. The retinal tissue is infiltrated with huge dark cells where the tumour has broken into it. There is an outstanding polymorphism of these black chromatophores. Some are like typical clump cells of the iris, roundish, like amoebae which have drawn in their pseudopodia, others show

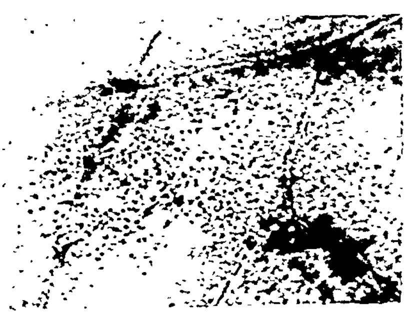

FIG. 10.

Case of malign melanoma of ciliary body and choroid. Retina peeled off and cleared (Hem.—150×). The pigmented cells are spreading within the retina especially along the retinal vessels.

branching processes. The granules are brownish to deep black. The chromatophores look different from those seen in bulk specimens of retinitis pigmentosa or chorioretinitis syphilitica. The propagation occurs along retinal vessels predominantly although free "clump cells" are frequent. Even massive migration along vessels (Fig. 10) can be demonstrated. Treacher Collins (1926) mentions in his report on "Melanomata of the Eye" this Ginsberg type of clump cells which rise from chromatophores undergoing malignant degeneration. This change of large branching uveal chromatophores into spherical or polygonal deeply pigmented cells without processes occurs according to Treacher Collins during a phase of deranged metabolism.

Bulk specimens of choroid are possible only at the outskirts of the melanoma, as no view can be achieved over a certain thickness of the specimen, even after long protracted depigmentation. Although the spindle-cell type predominates there a considerable polymorphism is to be observed. It seems that the different stages of contraction of the branched chromatophores are responsible for this polymorphism, for the explanation of which Treacher Collins' theory appears adequate. The amoeboid character of the chromatophores seems to be the main cause of the varying shape of chromatophores found with the melanomata, even in different parts of the same growth. Another reason is the reaction of the phagocytic reticulum cells engulfing pigment and other débris. These cells are protean, varying in shape, size and pigment content.

Finally, reference must be made to the special position of the hexagonal cells detached from this single layer. Pigmented epithelial cells are produced in great masses in many disorders of the uvea. They do not remain, practically, in a cell unit, as to create a kind of tumour, but are freed, swell, undergo fatty degeneration frequently and may extrude their whole content. This kind of production occurs at high velocity, as we do not usually discover any defect in the hexagonal layer despite the massive loss. Retinitis exudativa externa (Coats) is a typical example of this kind of hyperproduction and fatty changes, in which the mass of "ghost" or "bladder" cells might be taken for a blastomatous growth of this primitive layer, a blastoma as, *e.g.*, leukaemia is considered a tumour of the blood.

The true tumours of the hexagonal layers in the common sense might be expected in the shape of an epiblastic growth, a melanocarcinoma. We have seen, however, a growth of hexagonal cells in a case of dystrophia adiposa of the eyeball (Fig. 11), of undoubted fibromatous character. Here the fibroblasts grew out

from the hexagonal cells which produced therefore cells of mesodermal type. Here we want to stress the unique position of this primitive layer which remains, as far as can be observed microscopically, unchanged from early foetal life.

A similar behaviour of the epithelium of the lens capsule is recognized (Samuels, 1946 and otherwise) (Loewenstein, 1934), which produces under certain circumstances a fibroblastic tissue.

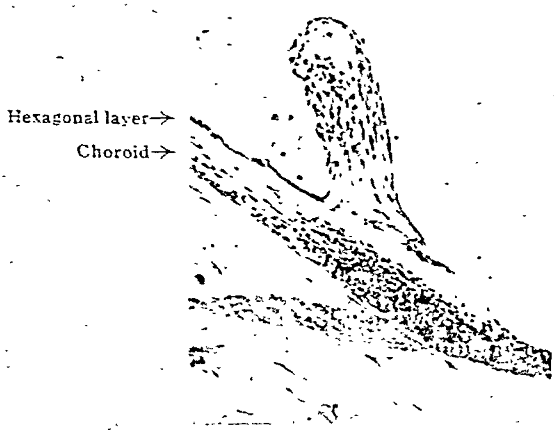

FIG. 11.

Dystrophia adiposa. H.E. 150×. The pigmented epithelium grows out into the fibroma-like tumour.

We conclude that hexagonal cells add a great variety of pigmented cells of very different shape to the pathological melanomatous growth in which even spindle-shaped units may be present. The presence of this type of cell, therefore, is no proof against the origin of a melanotic growth in the hexagonal layer.

SUMMARY AND CONCLUSIONS

(1) Naevi are generally inherited as are markings of domesticated animals (Meirowsky, 1942). They are developmentally arrested and often displaced tissues which might or might not, under unknown conditions, start multiplying from the point of development at which they have arrived. There is no basic difference between a naevus and a phakoma (Van der Hoeve).

(2) In tissues where these naevus cells produce pigment (melanoblasts), pigment granules are also stored in branched reticulum cells (melanophores).

(3) Pigmented naevi may be derived, as far as we know, from early stages of Schwann's sheath, from the primitive epithelium of the skin or from the outer layer of the secondary eye vesicle.

(4) No doubt exists about the epiblastic origin of the naevus mucosus cysticus of the conjunctiva.

(5) Pigmented naevus cell growth, at the margin of the lower lid, may contain, besides typical naevus cells, islets of epithelial structure and branched chromatophores.

(6) Naevus cell metabolism may set free growth-promoting factors responsible for controlled or uncontrolled new growth. These growth-promoting factors might be related to the melanins, being different from known carcinogenic substances.

(7) Distinction between innocent choroidal naevus and malignant choroidal melanoma is difficult ophthalmoscopically and histologically.

(8) The simultaneous presence of an identical pigmented melanoma in choroid and ciliary nerve is no proof of the origin of the blastoma from Schwann's sheath.

(9) There is a greater polymorphism of melanoma cells in flat sections and bulk specimens of melanoma invaded retina than in routine sections.

(10) Mesodermal structure of a pigmented malignant choroidal blastoma does not exclude origin in the hexagonal layers because out-growth from the pigmented epithelium may show typical mesodermal character. The unique developmental position of the pigmented epithelium, the outer layer of the secondary eye vesicle may account for this.

(11) The adrenalin melanoma is described clinically and histologically, and is explained, as is the conjunctival melanosis of the hydroquinon workers, by melanotic reticulosis. Although no malignant evolution is known, the corneal changes in hydroquinon damage are reminiscent of precancerous Bowen's disease. Adrenaline, hydroquinone and melanin are chemically related. Asthmatic persons receiving adrenaline for a long period ought to be observed carefully.

(12) Melanotic débris marked the path of elimination in cases of malignant melanoma of the iris. It is likely that the pigment granules in the trabeculum and vessels carry the tumour elements and show the course of the metastases. That might be a warning against "conservative" operation for localized malignant iris melanomata. Gonioscopic investigation of these cases before local excision of the melanoma is indicated.

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BLINDNESS ASSOCIATED WITH HAEMORRHAGE*

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DURING the syncopal phase which may accompany or immediately follow massive haemorrhage, it is not uncommon for the patient to complain of visual disturbances and even blindness. This condition is invariably brief and seldom exceeds one hour in duration. More often it only lasts a few minutes. Jones (1947) describes a typical case of this kind. (Also see Appendix.) Blindness of a longer duration and in most cases associated with permanent damage to the visual apparatus is a rare though well-recognised complication of massive and repeated haemorrhage.

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Although this latter variety of blindness may occur simultaneously with the haemorrhage, it occurs just as frequently after an interval of several days and even weeks. It would seem to be important to separate these two varieties of blindness in view of their different prognosis, and also in view of the fact that the former recovers with no therapy, whereas the latter variety has a uniformly bad prognosis in spite of treatment. These cases are not, however, clearly separated in the literature. It would seem that the former variety is associated with a rapid reduction in the blood-volume and a fall in blood-pressure. The latter or second variety would seem to occur when the blood-volume has returned to normal with the resulting fall in haemoglobin and plasma-proteins. However, there are other apparently essential requirements for the latter variety to occur, and they will be discussed more fully later in this paper. In the literature most of the described cases are of this second or delayed amaurosis, but for the purposes of the table in this paper they will all be grouped together, and where possible the date of onset after the last haemorrhage is given. Treatment has often been coloured by the physicians' ideas as to causation, and also limited by the means available to the earlier medical authorities who investigated the condition in any detail. Groenouw (1904) estimated that 25 per cent. of cases of amblyopia occurred during or immediately after haemorrhage, 20 per cent. occurred within 12 hours, and in more than 50 per cent. it appeared within three weeks of haemorrhage. Pergen (1896) said 21 per cent. of cases occurred simultaneously with the haemorrhage, 9 per cent. within twenty-four hours of bleeding, 51 per cent. within 7 days, 14 per cent. in the second week, and 5 per cent. in the third week. Terson (1922) from his collected cases gave 8·3 per cent. during haemorrhage, 11·6 per cent. immediately after haemorrhage, 14·2 per cent. within 12 hours, 19·2 per cent. within two days, 39·2 per cent. between three and sixteen days, and 7·5 per cent. after sixteen days.

The causal mechanism is obscure. It has been variously stated to be due to haemorrhage into the optic nerve-sheaths (von Graefe, 1860); ischaemic fatty degeneration of the optic nerve (Westhoff and Ziegler, 1899); retrobulbar neuritis (Hoffman, 1899); oedema and multiple haemorrhages (Leber, 1877); changed consistency of the blood (Wilbrand and Saenger, 1904); thrombotic foci causing degeneration (Goerlitz, 1920); toxins (Groenouw 1904, Terrien 1921, Kummel 1932, Rønne 1932, Holden 1899, and Duggan 1943). Duggan even identifies the toxin as adrenalin. Langdon (1933) believes that anaemia is the sole factor; Wolff (1935) gives arterial spasm as the cause; Hartmann and Parfonry (1934) blame vasoconstriction; acidosis, ischaemia and the effects of light (Roe,

1942); Cox (1944) thrombosis of the central retinal vein, and Fisher (1929) exudation of fluid into nerve-sheaths. According to Duke-Elder (1940) the mechanism in some ways resembles that of amblyopia due to quinine poisoning.

The main difficulty appears to lie in the fact that it is very seldom that eyes affected are available for detailed pathological examination, and then not at all at the very necessary phases in the evolution of the condition leading up to the fully developed optic atrophy.

There are numerous difficulties besetting all the above explanations, but the major difficulty appears to be to explain the late onset of the condition in so many cases. If severe anoxaemia is the cause, why does it not occur during or immediately after the haemorrhage in all or most cases; why does it so very rarely, if ever, follow massive haemorrhage in the healthy? Some authorities say that blindness never follows a single haemorrhage in a person in normal health. According to Zentmayer (1912) de Wecker, and according to Grout (1914) de Wecker, Kneis, Wilbrand and Saenger did not see a single case in the Franco-Prussian War, where visual disturbance could be attributed to surgical haemorrhage alone. Harbridge (1924) could find only 18 cases recorded in the literature between 1912 and 1924 and including the war of 1914-18. MacRae (1928) says that no instance of this form of sudden blindness was recorded in the 1914-18 war, although Terrien (1921) quotes one case. Goulden (1935) had seen records of two cases. Wolff (1935) quotes Pincus as having seen two cases following amputation.

It is probable that the amblyopia is not due to a single cause, that all the above factors participate in varying degree depending on the underlying local and systemic pathology. However, in view of our knowledge of the changes that occur in the blood after haemorrhage, it would seem that of all these changes, dilution of the blood by tissue-fluids is the one that is most likely to require some hours or even days to occur, and would most closely parallel the onset of the delayed amaurosis. In chronic illness, particularly if it is associated with recurrent small haemorrhages and restricted diet, not only would anaemia occur, but the plasma-proteins and the body-reserve of proteins would be much depleted.

If one of the important features in causing the ischaemic amblyopia to occur were oedema of the optic nerve, this might and could cause some compression of the entering, and even more of the leaving blood-vessels. We would expect this oedema to be more marked in the presence of low plasma-proteins, damage to capillary and vessel walls by ischaemia, acidosis, capillary vaso-dilatation, arteriolar constriction and compression of venules. A vicious

circle would thus ensue. The oedema fluid by compressing the outgoing veins would, if the blood were dilute and anaemic, cause an appreciable fall in the quantity of blood perfusing the retina at any instant. Holden (1899) found after experimental haemorrhage in dogs "changes indicating the presence of a non-coagulable liquid in the nerve fibre layer." Diffuse retinal oedema was also noticed by Goerlitz (1920), and oedema of the optic nerve was held responsible by Leber (1877) and Fisher (1929). Lehane (1941) quotes a case with chronic anaemia, gastro-intestinal in origin, in which transient total blindness lasting three hours occurred suddenly 15 minutes after transfusion had been completed at the rate of 2·0 c.c. per minute. Although he does not believe it is the cause, it is likely that sudden rapid increase in blood-volume above normal with resulting optic nerve oedema may have been the cause here. A similar case of post-transfusion blindness is reported by Jiron (1939).

There would thus seem to be several factors involved, each of which alone is incapable of causing the amblyopia. Anaemia alone does not appear to cause amblyopia, as common clinical experience indicates. Although optic atrophy has been described in pernicious anaemia (Cohen, 1936; Box, 1936; Panton, 1935; Kampmeier and Jones, 1938) it is extremely rare and may perhaps not be related to the anaemia but rather to the underlying sub-acute combined degeneration of the cord. Varying degrees of optic atrophy following retrobulbar neuritis had been noted in chlorosis or iron-deficiency anaemia by a few early authors (Gowers, 1904). Newton (1944) describes a case following anaemia not due to haemorrhage. Amblyopia in the nephrotic syndrome with its low plasma-protein and only mild anaemia must be extraordinarily rare, and we know that amaurosis following a single massive haemorrhage is almost unknown. A fortuitous association of these three factors would thus seem the most likely underlying mechanism. The haemorrhage presumably causes the initial though temporary generalised arteriolar vaso-constriction. The increased capillary permeability thus produced helps the other factors to set the entire cycle in motion.

If we accept the low plasma-proteins in the presence of anaemia as the essential background of the cycle, then we would expect, should the plasma-proteins be very low, sudden onset of blindness simultaneously with a sudden brisk though small haemorrhage. In other anaemic patients, in whom the plasma-protein level is not low, though tissue protein reserves are depleted, we would expect loss of sight to occur not at the time of the haemorrhage but in the post-haemorrhagic state, when the blood-volume is being made up by tissue-fluids, and hence plasma-proteins are being

depleted. Lastly, in fit, healthy, well-fed subjects such as young soldiers, even after severe haemorrhage, anaemia and blood dilution could not occur to the necessary degree causing the required fall in plasma-proteins and yet preserving life. Hence blindness does not arise.

In view of the variety of interest of this condition, two further personal cases are now described. A third case, of which full details are not available, is described in the appendix.

After the description of these two cases, the results of a survey of the literature from January, 1924, until mid-194[illegible] [illegible] in table form with a brief analysis.

CASE 1.—Mr. C. B., aged 58 years—a farm bailiff—was admitted to hospital with a history of haematemesis 18 hours before admission. [illegible] a well-covered man in moderately good physical condition; [illegible] per minute, B.P. 120/60 and haemoglobin 2·7 gms. Apparently he had [illegible] dyspepsia for some years, and a similar attack of bleeding [illegible].

A barium meal at this hospital three weeks after admission [illegible] of a peptic ulcer. His vision had been bad for some time [illegible] before admission it was definitely getting worse. Two weeks before [illegible] walked into a telegraph pole and thought it was the road."

Five days after admission he had a throbbing headache and complained [illegible] onset of blindness on the right side. The following day the field of vision of the right eye was restricted to the central part of the temporal field. The right pupil did not react to light. Cranial nerves were otherwise normal. On examination he was very pale, quite orientated, no tachycardia, B.P. 105/65. Heart normal. Urine contained a trace of albumin. Left pupil reacted to light, right pupil was dilated and much larger than left, irregular in outline with [illegible] light response. Both fundi showed slight swelling with marked pallor [illegible] the [illegible] the edges of which were indistinct, and faded imperceptibly into the [illegible] retina. In both eyes the veins were congested and the arteries narrowed and showed a marked light reflex with nipping of veins; there were no exudates and no [illegible] abnormality. Both eyes were presbyopic with limitation of field of vision [illegible] eye in all directions. But the right eye showed tiny linear haemorrhage streaks radiating out like a fan from the papilla.

1·35 litres of blood were given by slow continuous drip. Improvement of vision rapidly began and was maintained. The visual field in the right eye increased daily. On discharge six weeks after admission his right eye had improved considerably, but there was still some limitation of the field of vision in all directions. His haemoglobin was 11·5 gm.

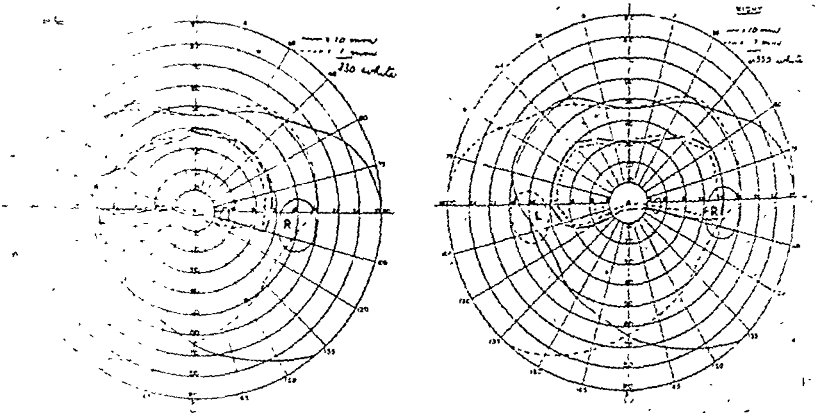
When seen six months later, both discs were rather pale, the right more than the left, but there was no definite evidence of optic atrophy. Vision was normal for him in the left eye, but the right eye had limitation of its field in all directions.

When heard of on August 29, 1947, four years after his first admission to hospital, he was still at full employment as a bailiff. He had no further haemorrhage or dyspepsia. He wrote and informed me that vision in his right eye was slight, but there was no apparent deterioration of the sight of his left eye.

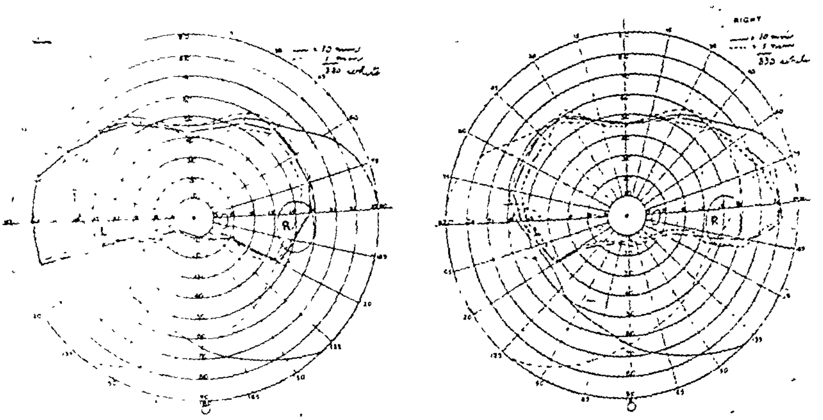
The patient was last seen on December 13, 1947. On that day vision in his right eye was restricted entirely to perception of light in the centre of the field. The right disc was evenly pale and showed a clearly demarcated periphery (optic atrophy). The retina appeared normal except for minimal arterio-sclerotic change in the arteries. There were no exudates or haemorrhages. The left eye showed presbyopic change but a normal fundus oculi.

CASE 2.—Mr. A. G., aged 71 years—a clerk—was first admitted to hospital May 31, 1946, after a road accident. He was discharged August 22, 1946, in a walking-cast, with non-union of his leg fractures. He attended as an out-patient

in the orthopaedic department, and was re-admitted June 26, 1947, with a progressive paraplegia of two weeks' duration. Investigation suggested that this was due to neoplasm. His prostate was large and hard. Formalin-stable serum acid phosphatase was first found to be 2·0 K.A. units. A later figure was 13·0 K.A. units. Treatment was begun with stilboestrol, but in spite of large doses there was no improvement. Laminectomy revealed compression of the cord by secondary growth, probably from the prostate. He developed a urinary infection, and had recurrent



Case II.—Before Transfusion.



Case II —After Transfusion

attacks of haemorrhagic cystitis which responded to alkalies, fluids and sulphanilamide. In spite of a suprapubic cystotomy this haemorrhagic cystitis recurred. On July 3, 1948, and July 4, 1948, he bled severely from his bladder—this lasted for 24 hours and then ceased. On July 5, 1948, his haemoglobin was returned as 3·7 gm. In the evening of July 5, 1948, he complained of failing vision. On the morning of July 6, 1948, his sight (both eyes) was very poor—he could not read and could just distinguish outlines. He was transfused with two pints of blood on the 6th and 7th July. On the 8th he reported that his vision had improved considerably.

Retinal change at no time was marked. There was only pallor of disc and retina, and 48 hours after transfusion the pale retina became more normal in appearance. However, the discs still looked pale. Except for slight arterio-sclerotic vascular changes, there were no exudates or haemorrhages. On July 13, 1948, his haemoglobin was 7·2 gm. and he could read the large print in the daily newspaper. His blood pressure was 160/80 mm. Hg and his blood urea 41 mgm. per 100 ml.

On July 22, 1948, both fundi appeared normal and he could read small newspaper print, though for short periods only. On August 7, 1948, further vesical bleeding occurred, his haemoglobin was then 4·4 gm., and there was further deterioration of vision. Bleeding ceased in 24 hours and visual recovery began again. Discs now definitely pale. A few hard exudates, arteries very thin; veins congested; no haemorrhages. On August 11, 1948, plasma-protein estimation gave the following result: total protein 4·5 gm./100 ml.; albumin 2·8 gm., and globulin 1·7 gm. Although these proteins are not very low, we feel that during the few days that elapsed after haemorrhage they have been made up from the tissue-protein reserve, as we have endeavoured to maintain this patient on a high protein and high calorie diet. What part bone secondaries play in the blood changes is impossible to assess in this case.

In view of the definite evidence of persistent renal and vesical infection in this case it may be thought that haemorrhage was not the only factor. The low blood-globulin is rather against any marked systemic disturbance of the blood-proteins by the infection. The close relation too between the bouts of prolonged vesical haemorrhage and loss of sight clearly showed that the key mechanism was the haemorrhage, and that at first the process was reversible. This patient later died. No further macroscopical vesical haemorrhage occurred, and no further visual deterioration. However, samples of urine always contained red cells. As we were at no time really able to control his urinary infection, this could not be the cause of the loss of sight, though it was an important accessory factor. The eye was not examined after death, as permission for autopsy could not be obtained.

In this case the main features would appear to be prolonged disability from fractures, paraplegia, carcinoma of the prostate with secondaries in the cord and elsewhere, chronic vesical infection and recurrent vesical haemorrhage. All these features together did not produce loss of sight until profuse bleeding occurred, necessitating transfusion. We feel, therefore, that this can legitimately be considered a case of loss of sight due primarily to haemorrhage.

Discussion

These two cases and the third case described in the appendix illustrate many features common to this condition. The causes are respectively, gastric haemorrhage, vesical haemorrhage and uterine haemorrhage. Out of 106 cases recorded up to 1876 by Fries (quoted by Barr, 1934), 36 per cent. were due to bleeding from the stomach, 25 per cent. due to uterine haemorrhage, and 25 per cent. due to blood-letting. In a survey of the literature from 1924 until the end of 1947 we were able to find 17 cases, including the three in this paper. (See Table.) Where it was possible to ascertain the cause the percentages were as follows: gastric haemorrhage and melaena 47 per cent. (20 cases), uterine haemorrhage 32·5 per cent. (14 cases), nasal haemorrhage 9 per cent. (4 cases) and miscellaneous haemorrhages 11·5 per cent. (5 cases).

Author	Year	Age	Sex	Lesion	Time of Onset (days)	Degree of Recovery of Vision	Source
JONES, F. A.	1947	56 70	M M	Gastric Haem. ,, ,,	8 Immediate	— —	*Brit. Med. J.*, **2**, 477. *Ibid.* **2**, 477.
BLACK, J.	1945	53	M	Haematemesis and Melaena	—	—	*Ibid.* **2**, 920.
COX, R. A.	1944	22	M	Trauma	?3	—	*Arch. Ophthal.*, **32**, 368.
LONG, A. E.	1943	52	F	Epistaxis	6	—	*Amer. J. Ophthal.*, **26**, 1179.
RØE, O.	1942	66	M	D.U. Melaena	2-3 weeks	Nil	*Acta Ophthal.*, **20**, 48.
TIDY, H. L.	1941	30	F	Post-partum	11	Complete recovery	*Brit. Med. J.*, **1**, 774.
BUSHPAN, A. ...	1941	—	F	Post-partum	—	—	*Vestnik oftal.*, **18**, 325.
ROBERTSON, C. K.	1941	55	M	D.U.	—	—	*Edin. Med. J.*, **48**, 414.
GIQUEAUX, R. E. ...	1941	—	—	—	—	—	*Anh. argent. de oftal.*, **2**, 155.
BAMFORD, C. H. and BARBER, H....	1940	46	M	Haematemesis	5	—	*Lancet*, **2**, 715.
MITTELSTRASS, H.	1938	26	F	Post-abor.	—	Partial	*Deutsche med. Wochenschr.*, **64**, 936
WAUTERS	1938	—	F	Post-abor.	—	—	*Bull. Soc. belge. d'opht.*, **76**, 59.
RUGG-GUNN, A. ...	1938	47 23 18	M M F	Haematemesis ,, Uterine H.	3-4 — <1 week	Nil Nil Slight	*Proc. Roy. Soc. Med.*, **31**, 665. *Ibid.* **31**, 665. *Ibid.* **31**, 665.
TATARZYNSKA, H.	1938	—	—	—	—	—	*Polska gaz. lek.*, **17**, 338.
DUGGAN, W. F. ...	1936	23	M	Blood Donation	2 weeks	Nil	*Arch. Ophthal.*, **16**, 380.

KORZHENYANTS, S.F.	1935	—	—	—	—	—	*Sovet. vestnik oftal.*, **7**, 391.
HARTMANN, E. and PARFONRY, J. ...	1934	—	—	Melaena	—	Partial	*Bull. Soc d'opht. de Paris.* Feb. 54.
BARR, A. S.	1934	32	F	Post-abor.	Several days	Partial	*Amer. J. Ophthal.*, **17**, 396.
GOLDFEDER, A. E. and *RAPOPORT K. N. (Fuchs case) ...	1934	29	F	Post-part.	Immediate	Recovered	*Klin. Monatsbl. f. Augenheilk.*, **93**, 666.
HARTMANN, E. ...	1933	—	—	—	—	—	*Bull. Soc. d'opht. de Paris.* May, 347.
LANGDON, H. M. ...	1933	39	F	Uterine H.	1 week	Partial	*Arch. Ophthal.*, **10**, 99.
de SCHWEINITZ, G. E.	1933	—	F	Post-abor.	6	Partial	*Ibid.* **10**, 102.
HERMAN, M. ...	1933	—	F	Post-abor.	—	—	*Ibid.* **10**, 102.
LANGERON	1933	64	F	Venesection	Immediate	Nil	*Lyon méd*, **152**, 176.
WEIL, P. E., BOUSSER J. and HALBRON, P. ...	1933	70	M	Nasal haem.	2	Partial	*Bull. et mém. Soc. méd. d. hôp. de Paris*, **49**, 386.
LAPORTE, A ...	1932	—	—	Haemat.	—		*Prat. méd. franç.*, **13**, 727.
GENET, L	1931	40	F	Miscarriage	10	Nil	*J de méd. de Lyon*, **12**, 585
SATANOWSKY, P ...	1930	22	F	Piles.	1	Slight	*Semana méd*, **2**, 956
		30	F	Uterine haem.	25	Slight	*Ibid* **2**, 956
WHITING, M.	1929	10	M	Melaena	—	Nil	*Tr Ophth. Soc. U.K.*, **49**, 141
		48	F	Melaena	—	Nil	*Ibid.*
		47	M	Melaena		Slight recov	*Ibid.*
		41	M	Haemat	3-14	Nil	*Ibid*
		18	M	Haemat	7	Nil	*Ibid.*
LISTER, A. E. J ...	1929	—	F	Uterine H.	2-3 weeks	Complete	*Ibid.*

Author	Year	Age	Sex	Lesion	Time of Onset (days)	Degree of Recovery of Vision	Source
GOULDEN, C ...	1929	18	M	Melaena	—	Nil	*Tr. Ophth. Soc. U K.*, **49**, 151.
COYON, A., CERISE, CLOG, W.	1927	—	—	Gastro-Intestinal	—	—	*Bull. et. mém. Soc. méd. d. hôp de Paris*, **51**, 53.
GRIMMINGER, W....	1925	38	M	D.U. Melaena	—	—	
		21	M	Epistaxis	—	—	*Z. f. Aug.*, **57**, 106.
HARBRIDGE, O. F....	1924	40	F	Epistaxis	1½	Mod.	*Amer. Jl. Ophthal.*, **7**, 192.
TERRIEN, F	1930	58	F	Haematemesis	9 days	Slight	*La Presse Médicale*, **2**, 954.
LOCKET, S.	1948	58	M	Haematemesis	6	Partial	Present article.
		71	M	Vesical Haem.	1	Partial	
		25	F	Post-abor.	Immediate	Complete	

* These authors quote another case which I have not included in the series in view of considerable doubt. A farmer's wife aged 34 years said to have lost her sight four days after uterine haemorrhage. Transfused with 440 c.c. of blood four months after onset of amaurosis with ophthalmoscopic optic atrophy. Apparently, however, she almost completely recovered and her optic atrophy disappeared. At the time of the transfusion her haemoglobin was 66% and her R.B.C. 4,810,000.

ANALYSIS :

Total No. of cases : 47.

Age Range : 18–71 *years.*

Site of haemorrhage :

Gastric Haem. and Melaena ... (Male 15, Female 2)	20
Uterine Haem.	14
Nasal Haem.	4
Misc. Haems.	5

Time of onset of blindness after last haem :

Immediate 4	
Within first week 15	= 15%
Within second week 5	= 56%
Within third week 2	= 18%
After third week 1	= 7%
	= 4%

Sex Ratio : 20 males to 20 females.

Recovery :

Complete 4	
Partial 14 (5 only slight recovery)	= 14%
Nil 11	= 50%
	= 36%

Age :

12 under 30 yrs. (7 females)	= 34%
18 under 40 yrs. (11 females)	= 51%
17 over 40 yrs. (13 males)	= 49%
11 over 50 yrs. (7 males)	= 31%

The ages of the three cases were respectively 58 years, 71 years, and 25 years. Terson gives the age range as 2 years to 77 years, but most commonly over 40 years. In the group from 1924 to 1947 the age range was 18 to 71 years. Classically the condition mainly affects males. In our collected survey there were 20 males to 20 females, but in the very small group confined to amblyopia from gastric and duodenal haemorrhage, including melaena, the ratio was 15 males to 2 females. In my own unpublished series of 189 cases of gastric and duodenal haemorrhage the ratio of males to females was 124 to 65. This indicates that in the group of blindness due to gastric haemorrhage males are more likely than females to develop blindness.

The extent of recovery of sight is variable. In the three cases described, one developed almost total blindness in one eye. The second case improved considerably, but he relapsed with further vesical haemorrhage, whereas the third case recovered completely. According to Tidy (1941) in 33 per cent. of all cases there is complete blindness, in 50 per cent. no improvement from maximal loss, 10 per cent. recover good or complete vision, and 7 per cent. show a variable degree of improvement. Singer's statistics were—not improved 45·9 per cent., improved 39·1 per cent., complete recovery 13·5 per cent., recovery with subsequent failure 1·5 per cent. Terson (1922), however, put the figure of permanently blind at 50 per cent. and Pergen (1896) at 54 per cent. Loss of sight is bilateral in 85 per cent. of cases (Duke-Elder, 1940).

The retinae usually show marked pallor and venous congestion. Much less frequently papilloedema, venous stasis and haemorrhages occur (Hurst, 1929), but the retinae may be completely normal without any vision being present. Later the disc becomes increasingly pale, the arteries fine and narrow, and optic atrophy becomes ophthalmoscopically evident. When loss of vision is permanent, it is due to optic atrophy (von Graefe, 1860).

Treatment would seem to be a full diet, including adequate protein intake, in all those chronic diseases in which haemorrhage may occur. Should haemorrhage occur, immediate transfusion of whole blood is advisable. When transfusion has not been available during the early stages, then slow transfusion with packed red cells is indicated.

Summary

(1) The early literature and aetiology of blindness following haemorrhage are briefly surveyed.

(2) Three further cases are described.

(3) An analysis of the cases in the literature from 1924 to 1947 follows.

APPENDIX

Mrs. "X," a young thin woman aged 25 years, was seen while bleeding from an abortion. She was pale and appeared almost exsanguinated. She had evidently been bleeding for some days. Ten minutes earlier she had a severe vaginal haemorrhage, and complained that she was unable to see. Rapid evacuation of her uterus was carried out, and the bleeding ceased. After she had been laid flat on her back with the foot of the bed elevated, she rapidly recovered her sight. In all she was apparently blind for 30 minutes.

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SOME OBSERVATIONS ON THE CAUSATION AND ELIMINATION OF SATTLER'S VEIL*

BY

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IN reading this paper, I lay no claim to any new or original theory on the causation of corneal veiling. On the contrary, it is my opinion that there has been too much theorising on this subject and all too little attention paid to the practical side of the subject of fitting with which, I believe, the causes of veiling are inextricably bound up. My aim in this address, therefore, will be to impart my views on the commoner errors in *fitting* which I have found to be constantly present in those cases in which veiling occurs to any appreciable extent. In doing this I shall appear firstly to be departing from the main subject of this paper, namely, corneal veiling; and secondly, to be making an attack on the methods of fitting of certain other practitioners and other types of lenses than moulded lenses. If I convey the latter impression, I offer my apologies in advance and hasten to justify myself on the grounds that, as in all other techniques which aim at precision, there is always a correct and incorrect method of approach.

As a preface to the statements I have to make, I would like to offer some justification for the decided views I hold. I first studied the methods of fitting moulded lenses under Dr. Joseph

* A paper read to the Contact Lens Society on February 21, 1949. Received for publication, March 25, 1949.

Dallos in 1938. At that time it was not unusual to require as many as 20 fittings and 6 to 12 fitting shells before a satisfactory final lens was obtained. Type-glasses were used as the starting point because the use of negocoll and the methods of moulding in those days gave such unsatisfactory results. Naturally, many prospective contact lens practitioners, finding the moulds so unsatisfactory, and not having had systematic instruction in the methods of modifying and fitting moulded shells, preferred to confine their practice to preformed lenses; and around this latter type of lens, a new and (I think) spurious "science" has grown up. I say this advisedly. Innumerable papers have been read and articles written which have absolutely no *practical* value. The mathematics of contact lenses has been delved into and imposing formulae thrust upon the unfortunate student of the subject, who must surely have formed the impression that he will not be able to fit lenses unless he masters these formulae, which is, of course, quite untrue. There have even been tables and slide-rules devised to give the power of contact lens correction which exactly corresponds to a given spectacle correction, to two decimal places; all this in spite of the fact that vertex distance is by no means the only factor in deciding the contact lens equivalent and that only the very best of technicians can work to such fine limits. It is not uncommon to hear or overhear discussion between contact lens practitioners as to the overall dimensions of the lenses they fit, their attention being directed toward a comparison with the dimensions of one colleague's lenses rather than a comparison of the lens with the eye it is meant to fit. All this I mention to show the unfortunate and deplorable tendency to create the spurious and entirely unpractical science to which I have already referred. Throughout the past ten years I have confined my attention to the fitting of moulded lenses and can now claim to be able to fit these lenses in one or two sessions of actual fitting, and to be able to eliminate corneal veiling in my cases. I therefore trust that I shall not be unduly criticised for the expression of decided opinions on this subject.

Among the theories put forward to explain the phenomenon of corneal veiling by contact lenses are that it is due to:

1. Embarrassment of the limbal circulation.
2. Unsuitability of the buffer solution used—(*a*) in its crystalloid content and (*b*) in its pH.
3. Interference with gaseous interchange at the cornea.

The matter of circulatory embarrassment was soon disposed of by providing what was considered adequate limbal clearance. Indeed, in certain quarters, limbal clearance is carried, as a

routine practice, to such an extreme that the bearing area of the scleral portion of the lens is reduced very materially and the optic occupies almost the entire lens. And still veiling occurs. It is hardly surprising, therefore, that the attention of investigators is so steadfastly turned in other directions in an endeavour to solve the problem of misting. It is in this latter departure that, in my view, the mistake lies. Exhaustive research in this country, and by whole teams of investigators in the United States of America, have led only to the conclusion that (1) the pH of the buffer solution undergoes a change towards the acid side by prolonged contact with the cornea (which, incidentally, should never be the case in a well-fitting lens), and (2) that wearers of contact lenses must conduct their own investigations into the optimum solution for their own particular needs. All this is leading exactly nowhere but is serving to make the wearing of contact lenses a subject of ever-increasing burden and complexity, whereas it should, after all these years, have been greatly simplified. The one line of investigation which calls for skill rather than science has been culpably neglected.

With reference to the rôle played by the buffer solution in causing irritation or veiling, or both, it appears to me to be wasted effort to investigate this matter because, undeniably, in a good contact lens the buffer solution should be entirely replaced by the tears in 15 to 20 minutes. This can be demonstrated quite easily and I shall undertake such a demonstration with pleasure whenever called upon to do so.

If the wearing of a contact lens were to cause misting by interference with gaseous interchange, why is misting not present on waking from sleep or after prolonged unconsciousness? I will not dispute the observation that prolonged contact of buffer solution with the cornea results in its absorption of CO_2 and consequent change in its pH. But, as I have already stated, such prolonged contact is certain evidence that the lens is unfit to be worn.

During the past three years I have made careful examinations in my practice of all lenses which have caused misting, and have compared them with those which were known to give rise to little or no veiling. Each lens was carefully palpated as well as examined *in situ*. Many of my colleagues, when handed a lens, will reach into their pockets for a vernier with which to measure the overall diameter and learn absolutely nothing about the lens except that it is larger or smaller than those he is able to fit. When I am handed a lens, I run my finger over the inner surface of the scleral portion and I derive much useful information about the lens and about the practitioner who fitted it. Every one of

the lenses which caused veiling exhibited one or more of the defects which I am about to describe, and when these defects were, for experimental reasons, only partly corrected, there was a partial improvement as evidenced by the ability to be worn for longer periods without misting and with less discomfort. Further correction of the defect led to further clinical improvement, and finally their complete eradication made trouble-free wear possible for twelve hours or longer. I shall now proceed to an account of the ways in which contact lenses may, in fitting badly, give rise to corneal veiling, and I propose first to touch briefly upon preformed lenses.

The original Zeiss-type lens must, of necessity, have a narrow haptic and consequently a small area of actual contact with the eye. Since the stability of a contact lens depends primarily on

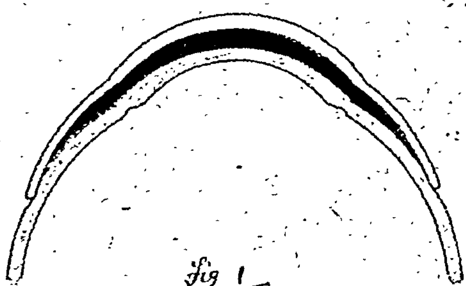


Fig 1

the capillary action of the film of fluid between it and the eye, it follows that a lens with a narrow scleral segment will be relatively unstable in accompanying the movements of the eye. It has therefore been, and still is, the custom to keep these lenses tight at the periphery in order to reduce their mobility (Fig. 1). This has the double effect of creating circulatory obstruction and imprisoning the buffer solution so that the original solution may be retained in the precorneal space for the whole period of wear. Its pH is thus liable to considerable change, due to absorption of CO_2. I am neither supporting nor refuting the suggestion that changes in the pH of the precorneal fluid play any part in veiling, but a stagnant pocket of fluid, in prolonged contact with the cornea, is decidedly unphysiological and is to be avoided, quite apart from the indication it gives of bad fitting.

Now, because of the narrowness of the scleral portion of the Zeiss lens, the method of dry fitting is not easy to apply and

the otherwise less satisfactory fluorescein method must be substituted. I maintain that the fluorescein method, often unreliable, is particularly unreliable at the corneo-scleral junction, and in an effort to avoid fitting a peripherally tight lens and its attendant

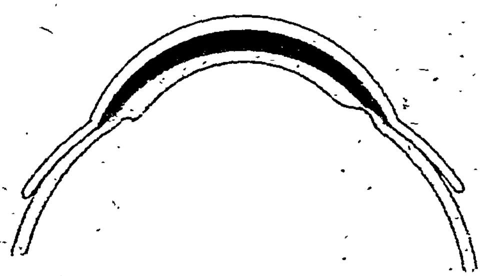


Fig. 2.

consequences, it is a very easy matter to swing to the other extreme and fit a shallow lens (Fig. 2). Clinically the results may be identical with those described above, except that the zone of circulatory embarrassment is moved to the corneo-scleral junction and impairs not so much the circulation itself as the process of

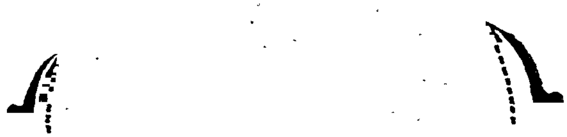


Fig. 3

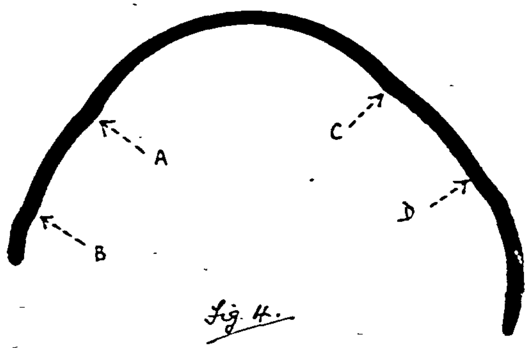
drainage of the corneal fluid into the bloodstream. The effect on the cornea will be much the same and stagnation of the precorneal fluid also occurs. It may be argued that the final limbal clearance given by the technician will eliminate this, but it serves only to move the ring of contact a fraction farther out.

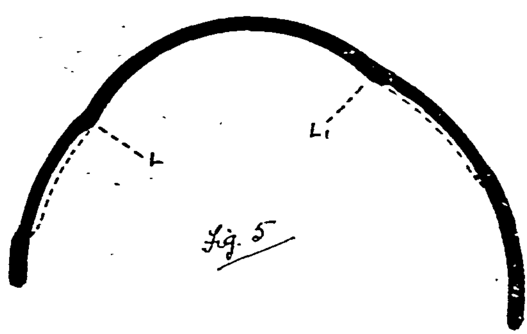
Let us now pass on to consideration of moulded lenses and turn our attention first to a study of the plaster cast obtained from an average good mould (Fig. 3). The corneal portion and a

zone 5 to 8 mm. wide immediately surrounding it will be a fairly accurate representation of the corresponding parts of the eye. But in the vast majority of cases the peripheral part of the cast will show elevations caused by folds of the conjunctiva of the fornices. Even when special measures are taken to avoid such folds, and the resulting cast appears to be free from them, careful inspection under oblique illumination will reveal some elevation at the periphery. There is likewise a very constant narrow elevation immediately around the corneal portion. The almost constant presence of this annular eminence, which has no visible counterpart on the eye itself, is of the first importance in the study of corneal veiling, for it can only be produced by heaping up of the conjunctiva in this region, and it indicates that either by swelling or by mechanical movement of the conjunctiva, or both, there is a noticeable tendency for the conjunctiva to move towards the limbus even in the very short time and very light pressure involved in the taking of a mould. This matter will presently be mentioned more fully. Before the plaster cast is sent to the technician, it should, of course, be modified to remove the elevations and restore continuity with the normal curve of the more central portion of the cast, both in the antero-posterior plane and in the frontal plane, making due allowance for the usual prominence found in the upper temporal quadrant, and for the upper and lower nasal "shoulders" consequent upon the more or less sudden transition from a lesser to a greater steepness of the scleral curve on the nasal side. If modification of the plaster cast is skilfully and adequately carried out, there is no reason why a shell made from it should need more than smoothing on its inner surface to effect successful fitting. The arrival at this happy stage in one or two sessions of fitting should not be the result of a fluke, nor need it provide occasion for celebration. It should and can be a consistent occurrence. The usual failing is to remove too little or none at all of the redundant plaster surface, and then to assume that the resulting shell is ready for finishing.

An inadequately modified plaster cast will yield a shell like that illustrated in Fig. 4. That portion of the shell between A and B or between C and D will follow the contour of the eye, whilst beyond B and D the shell will stand away from the eye. Now, the pressure of the lids on the loose periphery of the shell will cause heavy contact in the accurately fitting circum-corneal zone. We are now faced with two alternatives. If the periphery is very loose, the plaster should be further modified and another shell requested. If, on the other hand, the periphery is not very loose, the correct curve can be extended throughout by grinding

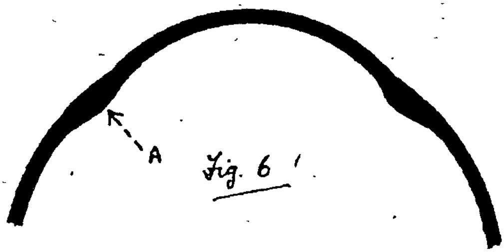
away the more central zone of the shell. This has the double advantage of saving a second shell and of reducing the *corneal* clearance created by the technician when the inner corneal surface was given a uniform radius of curvature. The process of grinding down the inner scleral surface must be carried *right through to the margin of the corneal portion.* Usually this is

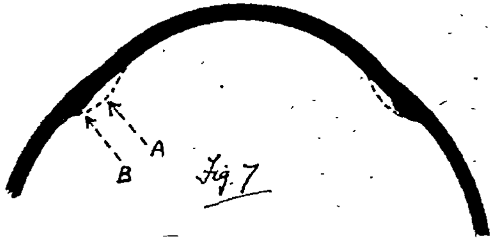




not done, and the result is that an annular " lip " (Fig. 5, L, L_1) remains so close to the corneo-scleral junction when the lens is *in situ* that no blanching is seen, nor will it be revealed by the use of fluorescein. It can, however, be discovered by passing the finger over the inner surface *from the periphery towards the centre* (a lip can always be felt if the finger is passed in the reverse direction), and by the process of dry fitting. Again, it may be argued that the lip will be removed when the limbal transition is made by the technician, but this is not necessarily so. If the lip is wide, as it might easily be, polishing the limbus will merely move the summit of the lip farther out (compare Figs. 6 and 7).

The effect of retention of this annular lip is, amongst other things, to set up the identical set of circumstances already





described in connection with preformed lenses, namely, circulatory embarrassment and stagnation of the precorneal fluid. Compare Figs. 8 and 9. With a well-fitting lens there should be capillary clearance over the whole of the surface (except where there is limbal clearance), and the capillary film of fluid should be in a constant process of replacement by the tears, so that the physico-chemical relationship between the cornea and the precorneal fluid is as near the normal as it could possibly be with a lens *in situ*. If, on the other hand, the lens has a "lip," as in Fig. 9, the first effect will be to cause the lens to stand off, and capillary clearance no longer exists anywhere. Later, pressure of the lids causes indentation of the eyeball, circulatory obstruction and closure of the precorneal space, so that the precorneal fluid stagnates. So consistently have I found this set of circumstances when veiling was present that, for ease of reference, I would like to name it. I would like to call it **"choked cornea."** The term is hardly less scientific than "choked disc," and I feel that the two conditions are not entirely dissimilar in their pathology despite their different aetiology.

There is yet another way in which "choked cornea" may be induced, even when no annular lip is present. Let us suppose that a lens has been completed which fits the eye perfectly, and in which there is limbal clearance which, at the time of final fitting, is considered adequate. And let us suppose also that the patient's conjunctiva is thick (as often happens) and tends to swell

readily with every stimulus. We have already seen that the mere insertion of the moulding shell into the conjunctival sac causes slight heaping-up of the conjunctiva around the cornea. Whether this is the mechanical shifting due to the very slight pressure involved, or due to swelling in reaction to the foreign body, is

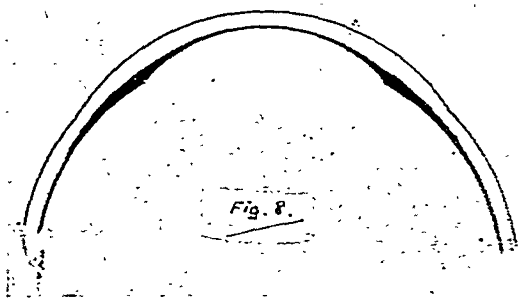


Fig. 8.

immaterial, because both these factors are present when the lens is worn. But if these factors, operating for several minutes, can cause sufficient heaping of the conjunctiva in this situation to be seen easily on the mould and plaster cast, how much more so will it occur after one or two hours of heavier pressure? The important point is that the conjunctiva *does* swell very con-

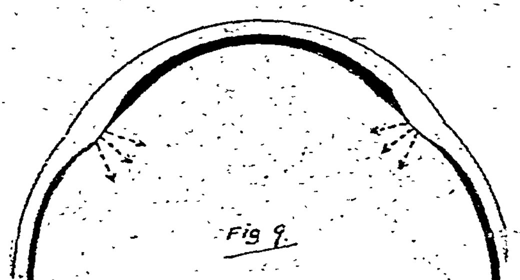


Fig 9.

siderably in many patients after a period of wear which varies with the individual case. It first becomes compressed against the scleral part of the lens, cutting off circulation of the tears through the precorneal space. It then spreads outwards and inwards, the latter movement filling up the limbal clearance and, probably, raising the pressure in the precorneal fluid. Later still, pressure of the conjunctiva on the globe will embarrass

the limbal clearance (compare Figs. 9 and 11). So once again we find all the requirements for the inducement of choked cornea. This will not be discovered unless the wearer is seen when the lenses are being worn and have been worn for a sufficient length of time to set up these conditions. It will not be readily discovered

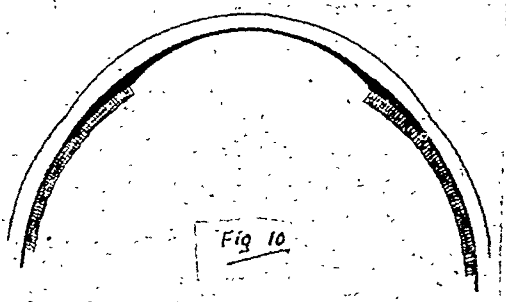


Fig 10

even then unless the lens is lifted carefully from its seat without actually removing it from the eye. To remove the lens straight away in order to re-insert it with fluorescein will mean the loss of all the evidence. If the wearer attends without having worn the lenses for the time requisite to set up misting, and the

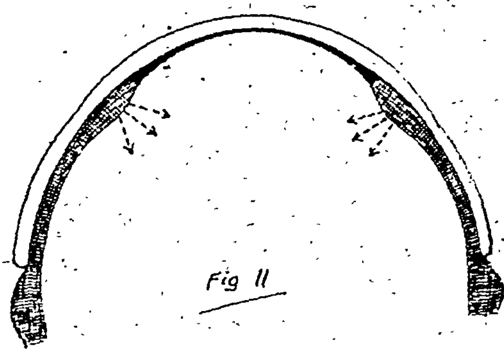


Fig 11

lenses are inserted at the time of examination, nothing at all will be found to account for the veiling, and the practitioner's attention will once again be directed towards consideration of the suitability of the buffer solution. The unfortunate patient will be sent away with yet another bottle of buffer solution to start the process of self-investigation *de novo*. Or recourse may be had to fenestration

as an easy way out of the difficulty. What an admission of bewilderment and failure this is!

It is my firm conviction that the set of circumstances to which I have referred as "choked cornea" is primarily responsible for setting up corneal veiling, and that the varying degrees of severity experienced are dependent on whether one or more defects are present in any given case. My conclusions may be summarised as follows:

Corneal misting is due to:

(*a*) Annular pressure on the globe by a "lip" or by excessive swelling of the conjunctiva.

(*b*) Stagnation of the precorneal fluid, especially when there is excessive corneal clearance.

When (*a*) is present, (*b*) is present also, and the result is veiling and intolerance.

(*c*) Excessive corneal clearance alone, *i.e.*, in the absence of any other defect, may cause veiling without discomfort because complete replacement of the precorneal fluid by the tears is a much slower process than when a capillary film of fluid is present. The fluid is thus exposed to absorption of CO_2 to a greater extent than would otherwise be the case.

This paper would not be complete without some reference to fenestration. I have no personal experience of fenestration in my cases because I have not had to resort to it. But I have, on many occasions, discussed it with colleagues, and have examined patients wearing fenestrated lenses. It would appear that in the early days of fenestration this procedure was applied to cases of severe and early veiling and, as is the case with all new and spectacular measures, the results were so startling that it was soon adopted by many as a routine practice. It is not surprising that such a simple method of overcoming the most difficult problem which besets contact lens fitters should soon become universally adopted. It served, however, more than any other single factor, to divert attention from the main subject of fitting, for if fenestration eliminates both veiling and discomfort, what else matters very much? This was followed by a fallacious line of reasoning. If one fenestration is good, two must be twice as good. And before very long we were to see or read of lenses with as many as twelve fenestrations, and what began as a contact lens ended by looking something like the top of a sugar castor. It was even stated that the tears would enter the precorneal space through certain openings and leave it *via* others. All that appeared to be missing were the sign posts which would ensure that the tears would follow the prescribed route! Such is

the nonsense which has been spoken, written and practised in the sphere of contact lens fitting. Obviously, when conditions illustrated in Figs. 9 and 11 exist, the drilling of a hole at the limbus will relieve the stagnation of the precorneal fluid and a certain amount of the circulatory embarrassment. Two or more holes will relieve the circulatory obstruction more effectively. But fenestration does not eradicate the underlying defects; on the contrary it diverts all attention from them and, in addition, introduces other evils hardly less distressing to the wearer than the misting. Add to all this the reluctant admission that fenestration does not always entirely eliminate veiling and we have all the data necessary to assess its true value. I now feel entirely justified in my persistent refusal to introduce this measure into my practice.

I will end this paper with a plea for more rationalism. Contact lens fitting primarily is an art and to a much less extent a science. To obtain, as nearly as possible, uniformly satisfactory results, one must fit lenses as *large as possible* consistent with free movement of the eye and this means moulded lenses, with capillary clearance *everywhere* except for adequate limbal clearance. This cannot be learned even from the finest text-books, but calls for patience and training under good supervision. There's the rub. So many prospective practitioners cannot, for economic or other reasons, take the necessary instruction, not realising that, once mastered, the technique of fitting this type of lens is so simple and satisfactory that they would not subsequently fit any other type. But it is so much easier, at first, to fit preformed lenses by following written instructions in a book, and the results are at least as good as those obtained with " moulded " lenses as fitted by the uninstructed. So we find that almost all contact lenses nowadays are either the Zeiss type (these are, surprisingly enough, still being supplied to patients!) or unsatisfactorily fitting " moulded " lenses, or the hybrid " modified " preformed lenses. Learned papers are read which are of academic value only, and a spurious science is growing up which is leading exactly nowhere. The reputation of contact lenses is, so far as the wearing public is concerned, rapidly going downhill, as it appears already to have done in the U.S.A., where all these unfortunate tendencies have been further complicated by the inherent dislike of any procedure calling for individual attention, and where the urge to mass-produce has given rise to the cone lens, the special curve lens and now the corneal lens. All these have had or will have their day, until it will no longer be possible to sustain the extravagant claims made for them. Only the properly fitted moulded lens will continue to give comfortable trouble-free wear and to maintain its well-earned reputation. It has been argued that these

lenses are too expensive to be available to the mass of prospective wearers and that some less expensive lens is needed. This argument is raised in support of the makeshift lenses which I condemn. My reply is that these lenses are no less expensive, either because their cost cannot or *will* not be reduced. It appears to me that the only way of making satisfactory moulded lenses available at the minimum cost is to have as many practitioners as possible who are trained to fit these in the minimum number of sessions of actual fitting. One could not hope to mass-produce dentures in order to reduce their cost. Why should we expect to achieve this in the realm of contact lens work?

Summary

Corneal veiling must not be treated as an isolated symptom but is inevitably bound up with the subject of fitting. It is due to defects in fitting which give rise to circulatory obstruction of varying degrees of severity, or to stagnation of the precorneal fluid, or to both. Stagnation of the precorneal fluid alone will give rise to slight veiling without intolerance, the veiling being usually only noticed in artificial light. When combined with circulatory embarrassment, veiling is more severe and is accompanied by irritability and intolerance. The remedy lies in correcting or avoiding the defects, not in relieving their consequences by drilling holes in the lens. All the untoward symptoms associated with contact lenses, veiling included, can be avoided by bringing the practice of fitting out of the academic and theoretical clouds down to solid earth.

A PRELIMINARY NOTE ON A NEW METHOD OF FIXING CORNEAL GRAFTS

BY

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AUCKLAND, NEW ZEALAND

I DID not intend to publish this small work until I had sufficient cases to demonstrate its usefulness or otherwise. With the present lack of donor grafting material in New Zealand, however, opportunity for these operations is infrequent; and as the method appeared so successful in the cases I have done, I decided to make this preliminary note.

In 1941 this method first occurred to me while considering the

technique of keratoplasty in general. It seemed to me that it would often be an advantage to have a fairly big graft (5 to 6 mm.). To get consistently good results and avoid anterior synechiae, one would have to aim at a water-tight joint. The ideal would appear to be perfectly clean-cut corneal discs of equal size from the donor and recipient, with no attempt at bevelling. If this were possible, the graft would fit like a plug, and would tend to be thrust out by the re-forming aqueous under intra-ocular pressure. There would be no tendency for it to go into the anterior chamber unless there was escape of aqueous allowing it to tilt. For these ideals a circular graft would theoretically be preferable to a square one.

This ideal would obviously be difficult to attain, and there would often be irregularities, at least in the deeper portion of the recipient cornea. Thus there would not always be a perfect fit, and so the aqueous would tend to leak. If the fit were perfect, the ordinary criss-cross sutures would hold the graft satisfactorily, and there would be no leak. With suture fixation, however, there would be nothing to prevent a leak at any irregular or weak point.

How then to improve on the existing methods of fixation in preventing aqueous leakage? The simplest method seemed to be to have something to cover the whole wound, slightly overlapping the cornea on each side and firmly fixed to the eye-ball. Some non-irritant metal unaffected by body fluids seemed most suitable. The idea was to have a ring made out of thin sheet metal 1·5 mm. wide, of such a circumference as to overlap the trephine cut by 0·75 mm. on each side, and with four arms 1·5 mm. wide to reach just beyond the limbus with notches cut near the ends of the arms for sutures tied round them to grip. The whole was to conform to the curvature of the cornea, the ends of the arms altering their curvature slightly as they came on to the sclera, where they were to be sutured, thus avoiding all sutures in the cornea.

My first experimental "corneal splint" was made of platinum. I made a cast of a rabbit's eye to which a thin sheet of platinum was moulded, and from which the splint was then cut. I experimented with dead rabbits' eyes, comparing this fixation with the various suture methods, and increasing the intra-ocular pressure by injecting saline. I also tried using egg-membrane between the cornea and splint as an extra seal against leakage, but the splint alone seemed to give sufficient closure. I was then preparing to do some research with live rabbits, but this was prevented by my being moved to another naval station, and I was unable to do any more until after the war. Then return to

civilian practice left little time for research, but eventually, after some further experimenting, I devised the present splints and trephine guides, which I shall describe.

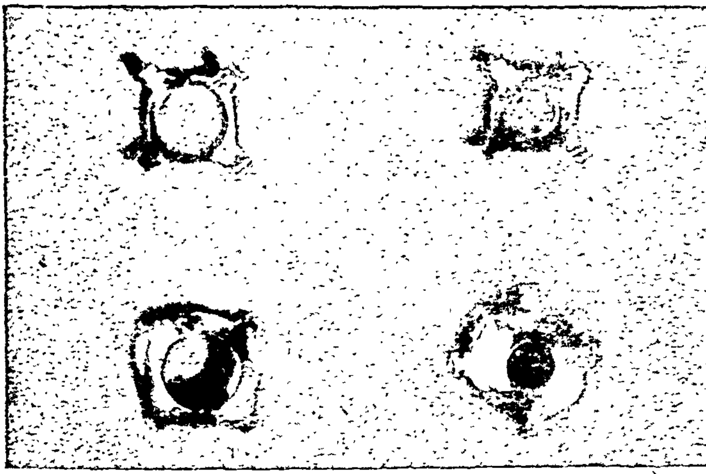

FIG. 1.

Top. Guide and Splint used in Case No. 2 (Corneal surface)
Lower. Guide and Splint used in Case No. 3. (Outer surface)

I have modified my original *splint*, shortening the arms so that they end over the cornea near the limbus. This is preferable to carrying them on to the sclera because

(1) Corneae vary in diameter, and also in length of different axes.

(2) It simplifies the making of the splint accurately, and leads to a better fit.

(3) There seems no contra-indication to placing sutures in the cornea well away from the wound, and in my experience they are more easily and more accurately placed than in the sclera with overlying conjunctiva.

Then there is the *trephine guide*, which is an essential in this method. It is an exact replica of the splint, except that the central aperture is enlarged so that it will just permit the entry of the trephine.

At operation the guide is first placed on the cornea. Then while it is held there, a suture is placed in the cornea beneath the end of each arm of the guide. These four sutures are tied once without completing the knot. This will hold the guide firmly in place. The trephine is then placed in the aperture in the guide

and a cut made—perhaps one-third of the way through the cornea. It is then removed, and the guide also removed after loosening but not undoing the suture-loops. The trephining is then completed in the usual manner. When the graft is put in place the splint is immediately applied, and the sutures tightened over the arms and the knots completed. We know that the splint will exactly cover the trephine cut with an equal overlap on each side without having to fit or measure it, because of the calculated association of the dimensions of the guide and splint.

The present splints and guides are made of platinized gold, and are of a thickness of 0·2 mm.

The pair used in case No. 2 were for a 4·5 mm. graft and of the following dimensions:

Splint—Internal diameter	= 3 mm.
External diameter	= 6 mm.
Overall diameter (end of arm to end of arm)	=10 mm.
Guide—As above except that internal diameter	= 4·75 mm.

As there was no apparent unfavourable reaction to the foreign body (splint), and the patient felt *no discomfort whatever*, it seemed to me that it would not matter if a larger area of cornea were covered by a broader splint. Thus one could make a *universal splint instead of having to have separate ones for each* size of graft. With the guides it might be best to have separate ones for each size of trephine, or else one could possibly use a guide for the largest trephine, and use collars to centre smaller trephines.

For case No. 3 the following splint and guide were used:—

Splint—Internal diameter	= 3·5 mm.
External diameter	= 8·5 mm.
Overall diameter (end of arm to end of arm)	=11·5 mm.
Guide—As above except that internal diameter	= 5·5 mm.

It will be seen that the above splint could be used for grafts between 5 and 7 mm. diameter, allowing a minimum overlap on the graft at one end of the recipient cornea, at the other of 0·75 mm.

NOTES ON THREE CASES OF CORNEAL GRAFT

I have only done three cases between December, 1947 and November, 1948, but they will serve to illustrate some points I have observed. In the first case I used sutures as described by Katzin (1947), and in the last two cases I used my corneal splint.

The first case gave me some anxiety, as he formed an anterior synechia. This,

however, I was able to free on the 18th day after the keratoplasty with a discission needle entered at the limbus without opening the wound. The graft did not become vascularised, but was slightly hazy from epithelial bedewing. The tension, however, was not appreciably raised to fingers—certainly not enough to account for bedewing as usually seen. Therefore I did not suspect glaucoma at

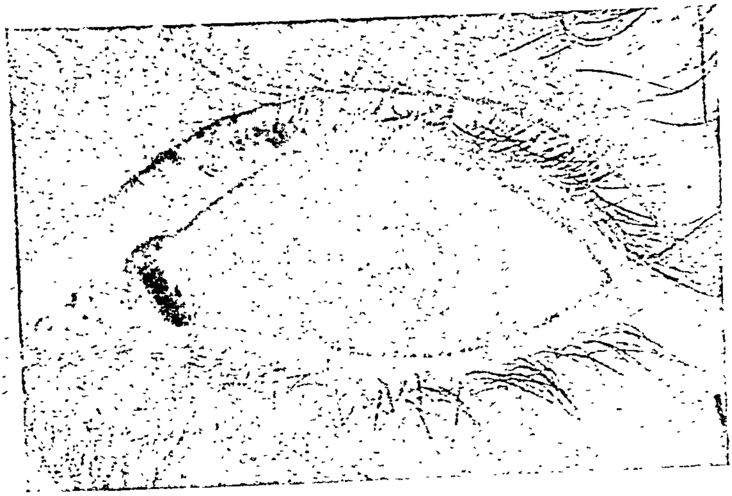

FIG. 2

Case No. 1. Fifteen months after operation Photograph poor, as it distorts the cornea and shows image of camera in centre of graft. Actually vision is 6/12 to 6/9 and Jaeger 1.

first but eventually I took the tension with a Schiötz tonometer, and found it to be slightly though definitely raised (30 mm. of Hg. as compared with 17·mm. in the other eye). I did a corneo-scleral trephine after which the cornea cleared completely, and the patient now has 6/12 to 6/9 vision with correction. It would seem from this that a corneal graft may be liable to develop epithelial bedewing at a considerably lower intra-ocular pressure than would a normal cornea.

FIG. 3.

Case No. 2. A, Before operation, showing dense leucoma, and B, one month after operation, showing clear 4 5 mm. graft.

The last two cases in which corneal splints were used have been uneventful, with excellent healing and quick re-formation of the anterior chamber. The third case was a 5 mm. disc, and after the trephine the iris contracted abnormally, so that the whole pupil and much of the iris lay within the trephine circle, but no anterior synechiae formed. That suggests quick reformation of the anterior chamber with *no appreciable leak.*

FIG. 4.

Case No. 3. One month after operation, showing clear 5 mm. graft. Note white marks near limbus indicating site of sutures that held splint in place.

Pain was absent, and there appeared to be no reaction to the splint in either case, nor was there any feeling of discomfort. In both cases the splints, when they were removed on the 7th day, were found covered by a film of mucus (a similar film was observed on the sutures in the first case) and there was no mark or indication as to where they had been touching the cornea. Therefore in future I think I shall be inclined to leave the splint on longer (ten days or more).

CONCLUSION

It seems to me that the following are the advantages of this method over other methods of fixing a corneal graft such as sutures, conjunctival flaps, etc.:—

(1) A more perfect sealing of the wound, together with prevention of tilting of graft.

(2) Prevention of sudden loss of anterior chamber after it has re-formed.

(3) Greater accuracy and even distribution of pressure over the whole wound.

(4) Simpler technique with assured perfect placing. The criss-cross sutures are quite difficult to place accurately so that they all cross in the centre and spread the pressure equally round the circumference of the graft.

(5) Nothing touches the central area of the graft, which is thus safe from possible injury, and a clear view is left of most of the graft and of the anterior chamber.

(6) I think it will be found that such strict rest for so long after the operation will not be necessary. With experience of more cases, I feel sure I shall be able to relax the restrictions with this method of fixation.

(7) It is appreciated that some cases for corneal grafting will have considerable astigmatism or flattening of the cornea, and it might be thought that this would militate against a good fit of the corneal splint. In reality this is not so, because when the four sutures are tied to the arms, the cornea is more or less made to conform to the natural corneal curve of the splint. In the third case some corneal astigmatism was actually observed, but that did not in any way interfere with the technique. If high astigmatism were encountered, the splint could be slightly bent to conform thereto.

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FURTHER INVESTIGATIONS ON THE ACTION OF DETERGENTS ON THE EYE *†

BY

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BRISTOL LONDON

INTRODUCTION

It is well known that the incorporation of wetting agents in drug solutions for local application enhances the penetration of the drug into the tissues (McKee *et al.*, 1943; Bellows and Gutman, 1943; Trim and Alexander, 1946). Ginsburg and Robson (1945) have shown that when dodecyl sodium sulphate is incorporated in solutions of sodium sulphacetamide applied to the cornea, the increase in penetration is due to an action of the detergent on the corneal epithelium. The action of the detergents on the eye has been further investigated and the results are described in the present communication.

METHODS

Penetration of drugs into the eye and the isolated cornea.

The methods used have been previously described by Robson and Tebrich (1943) and Ginsburg and Robson (1945).

Drop size measurements. There is a linear relationship between drop size and the surface tension of a solution provided that the age of the surface is constant (Gaddum, 1931). The size of drops formed at a water/paraffin interface was measured as follows: Ten drops of the solutions were delivered from a 5 ml. micro-burette with the tip immersed 1 cm. below the surface of liquid paraffin B.P. in a large crystallising dish. The total volume of solution delivered was too small to alter appreciably the level of paraffin in the dish so that the drops were formed under a practically constant head of paraffin. The time for delivery of ten drops was adjusted to 200 secs. and the volume of the drops delivered was measured.

Chemical Methods. Sulphacetamide was extracted from the tissues by the method of Bellows and Chinn (1939) and was estimated by the method of Bratton and Marshall (1940).

All experiments were performed on mature rabbits of both sexes and various breeds.

RESULTS

Table I shows the results of 36 experiments on the effect of five wetting agents on the penetration of sodium sulphacetamide into the cornea. In the experiments on the isolated cornea the drug was

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applied for 15 minutes, while in those on the intact animal it was applied for 6 minutes. The results clearly show that dodecyl sodium sulphate is the most effective of the detergents tested in increasing the penetration of the sulphonamide both into the living eye and into the isolated cornea. Thus 0·25 per cent. lissapol N increases penetration by 75 per cent., while 0·1 per cent. dodecyl

TABLE I

The effect of different concentrations of wetting agents on the penetration of 10 per cent. sodium sulphacetamide into and through the cornea.

Wetting Agent	Concentration gms. per cent.	Experiment	No. of Experiments	Conc. of Sulphacetamide mg. per cent.			
				Cornea		Anterior Fluid	
				+ W.A.	Control	+ W.A.	Control
Dodecyl sodium sulphate	0·1	Isolated cornea	3	803	357	29·5	8·3
,,	0·5	,,	2	1300	342	38·7	8·3
,,	1·0	,,	2	1915	315	54·4	6·9
,,	0·1	In vivo	6	349	191	29·1	6·4
,,	1·0	,,	1	860	200	77·2	16·1
Ammonium Lorol	1.0	Isolated cornea	2	886	478	17·6	8·9
Aerosol OT	0·1	Isolated cornea	1	434	—	6·9	—
,,	0·2	,,	1	451	449	8·5	7·6
,,	1·0	,,	3	398	365	10·2	11·6
,,	1·0	In vivo	4	389	108	32·3	8·0
Lissapol N	0·1	Isolated cornea	1	430	372	4·1	3·7
,,	0·25	,,	1	603	346	10·3	4·0
,,	0·5	,,	2	850	366	7·3	5·0
,,	1·0	,,	2	1050	295	19·8	4·7
,,	0·1	In vivo	1	114	186	4·2	8·7
,,	1·0	,,	1	601	155	84·9	13·3
C. 60799	1·0	Isolated cornea	2	288	323	2·3	2·6
,,	1·0	In vivo	1	48.8	61·9	3·3	5·5

sodium sulphate increases penetration by 125 per cent. C 60799 has no effect on the penetration of the drug. According to Bellows and Gutman (1943) aerosol OT is highly effective. In the present experiments it had no effect on the isolated cornea, but in the intact eye 1 per cent. of aerosol OT increased the penetration by 260 per cent. compared with 330 per cent. for 1 per cent. dodecyl sodium sulphate and 288 per cent. for 1 per cent. lissapol N.

Table II shows the penetration of sodium sulphacetamide with

aerosol OT into the eyes of anaesthetised rabbits and under the same conditions into the eyes of dead and cold rabbits.

In the living animal, aerosol OT increases the penetration of the drug, but has no effect when applied to the dead animal. The difference in the action of aerosol OT in the living and dead animals may be due to differences in temperature.

TABLE II

The penetration of sodium sulphacetamide with aerosol OT into the eyes of living and dead rabbits.

Tissue	Mg./100 gm. sulphacetamide			
	Living		Dead	
	S	S + A	S	S + A
Conjunctiva	135	416	704	568
Aqueous	8·0	32·3	3·5	4·3
Cornea	108	387	100	148
Iris	11·0	38·9	9·9	16·9
Sclera	42·0	100	42·1	30·2

The figures are the mean of 4 experiments.
S — 10% sodium sulphacetamide.
S + A — 10% sodium sulphacetamide plus 1% aerosol OT.

Two of the wetting agents, lissapol N and C 60799 (supplied by I.C.I), are non-ionic and therefore form stable solutions in the presence of high concentrations of sodium sulphacetamide, while the ionic detergents coagulate within an hour after the preparation of the solutions. The results on Table III show that 24 hours after the preparation of the solution the activity on the isolated cornea of dodecyl sodium sulphate is halved while that of lissapol N is unimpaired.

TABLE III

The effect of age of solution on the action on the isolated cornea of lissapol N. and dodecyl sodium sulphate.

Detergent, etc.	Sulphacetamide concentration in Cornea Mg./100 gm.	
	24 hr. old solution	Fresh solution
Lissapol N. 0.5%	668	696
Dodecyl sodium sulphate 0.5% ...	653	1240
None	—	334*

* The figures are the results of one experiment except the control which is the mean of 21 experiments.

In Table IV the effect of the wetting agents on the interfacial tension at a water/paraffin interface is compared with their effect in increasing the penetration of sulphacetamide into the isolated cornea. It will be seen that the order of the effect of the detergents on the interfacial tension is aerosol, lissapol, dodecyl sodium

TABLE IV

Effect of wetting agents on the interfacial tension at a water/paraffin interface and the percentage increase in the absorption by the cornea of 10 per cent. sodium sulphacetamide.

Wetting Agent	Percentage increases in absorption by cornea	IT. Water/Paraffin Vol. of 10 drops
NIL	0	1·79
Lissapol N 0·1%	14	0·095
,, 0·25%	74	0·071
,, 0·5%	170	0·063
,, 1·0%	290	0·060
Dodecyl Sodium Sulphate 0·1% ..	125	0·148
,, ,, 0·25% ...	—	0·138
,, ,, 0·5% ...	300	0 149
,, ,, 1·0% ...	510	0·144
Aerosol OT 1.0%	10	0·044

sulphate, *i.e.*, the reverse of their effects on sulphacetamide penetration. The interfacial tension of detergent plus drug solutions is not lower than the interfacial tension of solutions of the detergent alone, suggesting that in the concentrations used in these experiments, there is no tendency for complex formation between drug and detergent at the interface.

Effects of detergents on the living cornea.

A mucoid discharge on the surface of the cornea was observed when detergents were applied in concentrations, which increased penetration by 200 per cent. or more. After the application of 0·1 per cent. dodecyl sodium sulphate for 15 minutes *in vivo* the cornea stained with fluorescein, showing that the epithelium over the whole surface of the cornea had been damaged. Examination of eyes with the slit-lamp after six hourly application of drops of detergent solutions, showed oedema of the epithelium and punctate staining of the cornea with fluorescein confined to the anterior surface. These changes were more marked with 1 per cent. than with 0·1 per cent. dodecyl sodium sulphate. One per cent. lissapol N given in the same way produced a slight discharge and very

slight conjunctival oedema, these effects disappearing
Two successive hourly applications of drops of 0·5 per cent. lissapol N produced no abnormalities.

Discussion

The application of drugs with detergents to the eye enables the drug to penetrate the corneal epithelium and hence therapeutic concentrations may be established more rapidly and maintained for longer periods in the posterior layers of the cornea and in the anterior chamber. Of the detergents tested, dodecyl sodium sulphate is the most effective, but lissapol N has the advantage that it forms stable solutions in the presence of high concentrations of sodium sulphacetamide.

Trim and Alexander (1946) have shown that the effect of detergents in increasing the penetration of hexyl resorcinol into ascaris is due to the formation of a complex between the drug and the detergents, and that the order of effectiveness of detergents is the same as for their effect in lowering the interfacial tension at paraffin/water interfaces. In the present work, no evidence of compound formation between the detergents and sodium sulphacetamide was found, and the order of effectiveness of detergents in increasing the penetration of sodium sulphacetamide into the cornea is the reverse of their order for the lowering of the interfacial tension at paraffin/water interfaces.

The detergent increases the penetration of sodium sulphacetamide into the cornea by an effect on the corneal epithelium, possibly by solubilising the intercellular cement. After the prolonged application of detergents the epithelial cells may become completely dispersed. Detergents should not therefore be applied to the cornea for long periods and in high concentrations, and where the epithelium is damaged they offer no advantages as they only increase penetration through an undamaged epithelium.

Summary

The effect of five detergents on the penetration of sodium sulphacetamide into the eye was investigated. Sodium dodecyl sulphate was found to be the most effective.

There is no relation between this action of the detergents and their effect on the interfacial tension at a water/paraffin interface.

Effects of detergents on the cornea are described limiting their possible clinical uses, which are discussed.

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THE ARTIFICIALLY PRODUCED RETINAL PULSE

BY

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LONDON

IT is a well-known phenomenon that if the disc and its neighbourhood are observed while external presure is applied on any part of the globe, at a given moment the arteries in the disc start to pulsate. The artery empties and blanches corresponding to diastole, and fills up with blood corresponding to systole, or as Duke-Elder well puts it: " The blood column flashes across the disc." It is possible by greatly increased pressure to abolish completely the pulsation of the arteries on the disc—a procedure very unpleasant to the patient and rather dangerous. The veins on the disc are behaving in a peculiar way. When the first arterial pulsations appear on the disc, the venous pulse is accentuated, but usually does not change its character. With increased pressure on the eye, just before the arterial pulsation is completely abolished, the veins gradually become narrower, exhibit first a trickle of blood and then this trickle becomes beaded: finally the vein blanches completely. This is a summary of the general description of the artificially-produced arterial retinal pulse as given by such distinguished authorities as Baillart and Duke-Elder.

Some important details may now be added. Baillart (p. 28, ed., 1923) wrote that normally the retinal arteries look immobile. He mentions the opinions of Kummel and of Dr. Steyer. that they personally saw the pulsation of the light reflex (the retinal pulse), but not that of the central artery. I described some years ago that in red-free light one can easily see the pulse wave in nearly all primary and in some secondary branches of the central artery in a normal person, if the waves formed by those branches

are *sufficiently prominent. The same applies to the rare but* beautiful cases, where a primary branch of the artery forms a *partial ring* on the disc. This kind of pulse is easily explained by haemodynamics, and will not be considered in this paper. But if one applies very gradual pressure to the globe, one will first see a peculiar trembling of the arteries, difficult to describe, but very beautiful to behold. This trembling will be rhythmically intermittent and will correspond to the pulse wave. This is the moment, in my opinion, when the applied pressure plus the intraocular tension will be equal to the diastolic pressure of the central artery. The wall of the central artery will be unsupported; the diastolic pressure from inside will be equal to that from the outside, and the wall will contain that additional stimulus to extra contraction that is usually brought on by increased internal pressure, *i.e.*, this trembling is due to the vibration of the wall of the artery under the impact of the systolic wave. Let us increase our pressure a little, and the artery will start to collapse. This will start first deep in the disc on the proximal part of the primary branches, and it will spread to the periphery of the disc only with further increase of the pressure. The veins will become slightly narrowed, but their pulse will be accentuated. This is the level of the mean pressure. Baillart thinks that this is the level of the diastolic pressure, and that what we see is the vibration of the wall of the vessels. In my opinion we see the actual collapse of the artery.

Let us now increase the pressure still more, and watch the disc very closely. This flashing column of blood will reach the periphery of the disc and will be seen in the primary branches as well, not far from the disc, but with one great difference—the arteries on the disc are empty and, during the diastole, collapsed, to fill up in the systole; the same arteries on the retina will never collapse, although the arrival of the systolic wave can be actually seen. Why should it be so?

It is thus a strange fact that one can never collapse the retinal arteries, starting from outside the disc, even if the pressure is much higher than the systolic, and that the arteries on the disc will be completely empty and all pulsation will cease. These facts are not mentioned or described by anyone, except Baillart. He is emphatic about this—p. 39—" Cette observation (des vaisseaux) doit porter sur les artères sur le disc de la papille et non au delà." On page 51 he returns to that, and tries to explain it *en passant* " nous avons vus que les artères retiniennes ne battant que sur le disque papillaire; cela tient sans doute à ce qu'au delà du nerf optique elles sont incluses dans la tissue retinienne. . . . Quoi qu'en soit. . . . "

There is a definite law of hydraulics, that if pressure from outside is applied on any part of a ball full of liquid, inside this ball the presure will be equal in all directions. The eye is such a ball, with a not very elastic outside membrane—the sclera—with a scarcely compressible vitreous gel. Therefore the retina and the vessels will be under equal pressure everywhere, *mutatis mutandis*. Is the turgor of this tiny and fragile membrane such that, caught between the sclera and vitreous, even with the cushion effect of the uvea behind it, it will be able to stand *per se* a pressure higher than the systolic retinal pressure, even though the blood-vessels run only in one or two layers of the retina? It is hardly conceivable, however, and it is contradicted by the fact that the patient will notice a darkening of the field of vision—the best proof that the circulation is at a standstill. The possible explanation of this strange inability of the observer to collapse the retinal arteries, so much narrower on the retina than on the disc—and there they are collapsed—might be looked for, in my opinion, in a different direction.

If the pressure inside the eye is equal, then why should the collapse of the artery be seen first in the centre of the disc, not simultaneously on the whole of the disc? Because here the vessels are nearest to the acute angle formed by them on the disc. The greatest vascular obstacle to the pulse-wave will be this 90° angle —this is why we see normally the pulsation of the vessels on the retina if the waves are sufficiently prominent—and what we observe is the stoppage of the pulse in the main artery of the optic nerve, when the pulse-wave has to overcome the difficulty of penetrating the arteries on the disc passing through this acute angle.

If my reasoning is correct, then what we measure is not the diastolic pressure of the central artery at all, but that of the ophthalmic artery. So thinks also Duke-Elder (Vol. I, p. 707). Let us now see what is going on under the cuff of the sphygmomanometer when applied on the brachial artery. When inflation of the cuff is started the air, as is usual with gases, will try to form a kind of round ball in the middle of the rubber, and from then will spread gradually to the sides, so that the artery will be first compressed in the middle, and from then to its extremities up and down, leaving some small corners at the upper end, where the artery will not be completely compressed. Even before the level of the diastolic pressure is reached in the cuff (say 70 or 80 mm. of mercury) the venous pressure (17 cm. of water) will be overcome. Sainsbury argued (on proper theoretical grounds, that the colloids are incompressible and blood is a colloidal mixture), that really the artery under the cuff remains permanently patent.

It would be so, if the blood from the artery could not escape. But it does, and it goes not back toward the heart, but forwards to the periphery. The artery does therefore completely collapse, as it is seen to be doing on the disc in the eye. The venous stasis therefore starts in the arm before the level of the diastolic pressure is reached. *With increased pressure in the cuff a stream of* blood will reach the brachial artery from the subclavian, and an increased outflow from the brachial artery will go towards *the periphery*. It will be accommodated by opening up more capillaries in the periphery and their increased effort to expel the extra blood into the venous system. The veins will swell more, the cyanosis of the lower portion of the arm up to the lower edge of the cuff will increase, and the *venous pressure will rise enormously and quickly, being nearly equal to the systolic pressure* in the arteries. The patient will complain of severe discomfort. Take now a large-bore needle, and pierce the ante-cubital vein—the blood will pour in a strong stream from the needle; it will start to pulsate later on, and the discomfort of the patient will diminish. The whole circle of blood circulation is engaged, the capillary bed is widely open, the pressure in all sectors is nearly equal. The capillary bed—the great buffer, and very active in its own right as well—is the deciding factor in what was discussed. *This will explain what we see in the eye.*

When the arteries on the disc start to collapse and fill up, as mentioned before, the incoming pulse-wave with still more increased pressure can be followed, say a disc-diameter, *in the* primary branches, but these branches never collapse. Why do they collapse on the disc? First, because the blood column is still able to force itself a short distance to the periphery within the primary branches, as can be seen by red-free light. Secondly, because I believe that in the disc the vessels are under increased pressure, being already caught between the substance of the disc and the special membrane covering the disc and described by Krückman. But further to the periphery the blood column cannot flow quickly, as it has to meet and to overcome the great regulator-buffer of the retinal capillary bed. We see in the eye what we only imagined going on under the cuff of the sphygmomanometer, but with one difference. There is always an escape from the venous blood through the veins on the disc. That is why the venous *pulse is intensified in our experiments*; the veins become narrower and then collapse completely, while the entrance of the blood into the arteries is stopped by our pressure. With increased resistance the pressure in the ophthalmic artery rises (a well-known phenomenon of local angiospasm—a defensive reaction), the increased force of the pulse wave is transferred from the arteries

to capillaries and from them—partly passively but chiefly actively—to the veins. It is this constant pressure on the inside of the capillaries—a very active force—that prevents the retinal arteries from collapsing, no matter how great is the external pressure. Theoretically, if a large-calibre cannula could be introduced into the veins in the disc, so that venous blood could flow out independently of the intra-ocular tension, the arteries on the retina would probably collapse.

In the retina we have to deal with a specially constructed pressure system with one narrow entrance and one narrow exit. Why do not the veins become blackish and tortuous during this experiment? Tortuous or flattened, as in glaucoma, they could become, but the time is too short, and they are not diseased, as they may be in glaucoma. They cannot become blackish, because there is no permanent obstruction, as in thrombosis, neither is the venous pressure raised in the ophthalmic vein, as in asthma, etc.

When the artery collapses on the disc, but still remains full of blood on the retina, just outside the disc, what prevents the blood from trickling back to the disc during the diastole, and so prevents the artery from collapsing? Even immediately after death it does not happen, but the blood eventually trickles back towards the heart later on. In a boy who died from advanced aortic insufficiency, I saw it happen within a minute or two of his death. The arterial system is full of blood, and the *vis a tergo* is a combination of the heart action and that of the muscular wall of the artery, distended by the blood column and the pulse waves, always tonically contracted and prepared to close the artery completely, if opportunity presents itself. It is therefore the contraction of the muscular coat of the primary branches that moves the blood ever forward away from the heart, and does not allow any backflow.

Summary

A full description of the artificially-produced retinal pulse is given, and the impossibility is noted of collapsing the retinal arteries in contrast with those on the disc. This remarkable fact, hitherto observed only by Baillart, but not explained by him, is analysed and explained by the active buffer-action of the retinal capillary bed.

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FACULTY TOUR OF SCANDINAVIAN CLINICS

TWENTY members of the Faculty of Ophthalmologists, led by Mr. W. M. Muirhead, sailed from Harwich on June 10. When they disembarked at the same port on June 28, nearly every one had increased his girth, and all were richer in experience. No ophthalmologist could help being thrilled to see the hospitals where Rönne and Bjerrum did their work, and to stand beside Gullstrand's rocking-chair. That we should have been able, in little more than a fortnight, to visit six illustrious clinics, sail upon the Baltic, and walk in the garden of Linnaeus. is proof of Mr. Muirhead's genius for organisation. It was he who planned the tour, greatly to the advantage of his colleagues.

Denmark

Professor Ehlers and his assistants showed us the ophthalmic and some of the other departments of the Rijkshospitalet. After the professor had made a speech of welcome, he let us hear about some of the recent investigations pursued. Dr. Johansen described his pathological studies upon enucleated eyes, and Fru Braendstrup spoke of a method whereby the temperature of the superior fornix can be shown to exceed that of the inferior by about 0.75°C. A refinement of technique in scotometry was the subject of Dr. Holm-Pedersen's paper. His three-faced test-objects — black, white and red — keep the patient "on his toes," because the object can be made to disappear (*i.e.*, go black) anywhere on the screen. Dr. C. Edmund spoke of his preliminary research upon endogenous and exogenous factors governing the light-reflex of the cornea. Then came Mr. H. Campbell-Orr's fundus photographs and Mr. P. Jameson Evan's films showing (a) the insertion of a slip of the internal rectus into a paretic superior rectus, and (b) grafting of the outer halves of the superior and inferior recti into a paretic external rectus, together with recession of the internal rectus.

Professor Holm welcomed us to his department at the Kommunehospitalet, told us about the hospital's development, and demonstrated a number of cases. Dr. Erik Godtfredsen showed a case of naso-pharyngeal sarcoma complicated by left abducent palsy. No cervical gland metastases were found, but the diagnosis was confirmed by X-ray photographs. A case of bilateral uveo-parotid fever in a girl of 17 was also shown by Dr. Godtfredsen, who recalled with interest that Heerfordt was First Assistant in this clinic when he produced his classical description of uveo-parotitis 40 years ago. Dr. P. Braendstrup spoke about amblyopia, with special reference to its association with traumatic cataract, and he produced

statistics showing that amblyopia is seldom acquired after childhood. A case of siderosis was demonstrated by Dr. C. J. Möllenbach.

We also attended a meeting of the Danish Ophthalmological Society at the Domus Medica under the presidency of Professor Ehlers, who proceeded to confer honorary membership upon Sir Stewart Duke-Elder. Sir Stewart had also been created an Honorary Member of the Swedish Ophthalmological Society during its Annual Congress a few days previously. Papers were then delivered. Mr. R. C. Davenport spoke about glaucoma in association with high myopia, and Dr. H. Skydsgaard dealt with the problem of word-blindness. Mr. J. H. Doggart described several cases of central serous retinopathy, and Mr. C. D. Shapland produced an analysis of his results in the treatment of detached retina. Finally Dr. A. Lund described his experimental work upon the intra ocular circulation.

Sweden

Professor Larsson, who had recently returned from a visit to the United States, showed us his famous clinic in Lund, and described his researches upon lenticular metabolism by means of fluorescence estimations. He also testified to the value of anticoagulants—notably dicoumarol—in the treatment of retinal venous thrombosis. Other subjects considered by Professor Larsson were the extraction of non-magnetic intra-ocular foreign bodies, and the treatment of infantile epiphora. Dr. A. E. Maumenee's film of intracapsular extraction, and Dr. R. Townley Paton's film of keratoplasty for corneal scar and for Descemetocele were shown. Dr. G. Österlind discussed the effect of milk injections upon the intra-ocular pressure, and Dr. E. Palm gave an account of his studies on the permeability of the blood-aqueous barrier to various substances, including lipoids. Mr. P. McG. Moffatt reviewed the differential diagnosis of proptosis, and stressed certain prognostic difficulties. Senile massive exudate at the macular was the subject of a talk by Mr. R. C. Davenport, who pointed out that retinitis circinata is not a clinical entity, but rather an incidental feature of certain conditions—notably senile massive exudate at the macula.

At Uppsala Professor Berg is occupied with administrative work as Rector Magnificus of the University, but he nevertheless found time to welcome us and to lead the social activities. He delegated the task of showing us the Department of Ophthalmology to the acting professor, Dr. Gunnar von Bahr, who afterwards gave a thoughtful discourse on spherical and chromatic abberration of the eye, and their effect upon human vision. Dr. U. Halldén spoke about fusional phenomena in anomalous correspondence, and the possible influence of this factor upon squint surgically treated. Dr. E. Linner discussed the work of Ascher and Goldmann on aqueous veins, and

its relation to the measurement of pressure in the anterior chamber and in Schlemm's canal. Dr. K. H. Sjöström described a case of lightning-cataract, and reviewed the ocular changes arising from electric shock. An account of anterior lenticonus in a 19-year-old male was given by Dr. C. G. Åborg.

Professor G. Karpe, who has recently been appointed to the Chair of Ophthalmology at the Karolinska Institute, Stockholm, conducted us around its palatial hospital. He described his technique of electroretinography, and indicated ways in which this method of investigation can assist the prognosis, especially in cases of retinal detachment. Professor Karpe also showed some fundus photographs taken with the Nordenson camera, and we were afterwards privileged to meet Professor Nordenson himself. Dr. T. Kornerup described his investigations upon the living eye with the aid of spectrally restricted light. Various structures can be selectively displayed by green, red and other kinds of light, and he demonstrated the apparatus by which light is shattered by a prism, and the required spectral component filtered through a slit. Dr. K. O. Grandström received us at the no less palatial Södersjukhuset, and gave an account of his clinical observations upon cataract, glaucoma, arterial hypertension, intra-ocular foreign body and toxoplasmosis. Dr. W. Magnusson showed us some fine X-ray photographs.

At Göteborg, Dr. H. Rosengren spoke about his work on retinal detachment, and described his technique for injecting air into the vitreous. Afterwards he demonstrated this process on the operating-table. Mr. Harold Ridley gave a talk on tropical ophthalmology, and emphasised the appalling havoc wrought by onchocerciasis upon Central Africans. Dr. H. Sjögren's subject was keratoconjunctivitis sicca, whose causation is not yet fully understood, though infection and endocrine dyscrasia appear to be the principal agents. Dr. S. Holm also gave a talk on Sjögren's disease. Physiological optics was the subject of a paper by Dr. Stenström, and Dr. S. Holm underlined the importance of heredity as the main aetiological factor in refraction.

Norway

Professor Malling, who welcomed us at the Rikshospitalet, Oslo, performed two cataract extractions, and gave a talk on exfoliation of the anterior lens capsule. He maintained that, although such exfoliation is often associated with glaucoma, it is not these exfoliated particles which cause blockage of the filtration angle. Dr. M. Haarr spoke about periphlebitis as a sign of multiple sclerosis. This vascular change is ophthalmoscopically visible, he says, in the form of white infiltrates around the retinal veins anywhere except in the juxtapapillary region. Dr. O. Röe's subject was methanol-poisoning.

He mentioned the favourable effect of sodium bicarbonate administered in the first three days, and the influence of ethyl alcohol in restricting damage from adulterated liquor. Dr. H. P. Petersen stressed the possibility of extensive colloid degeneration in the retrobulbar portion of the optic nerve, and adduced such a change as the explanation for certain cases of field-defect associated with but explained only in part by colloid bodies ophthalmoscopically visible. He suggested the simile of an iceberg, whose hidden bulk is more menacing than its exposed pinnacle.

Conclusion

Mr. Muirhead would be the first to point out that no plans, however carefully laid, can set the seal of success upon a tour. Success can only be attained by the interaction of friendly hosts and appreciative guests. Let it therefore be stated—and stated emphatically—that nobody capable of gratitude could fail to be touched by the welcome extended to us by Dane, Swede and Norwegian alike. Scandinavian hospitality is proverbial, so that we had naturally expected to enjoy those Northern lands, but the result surpassed expectation. The heads of all six clinics, together with their assistants, senior and junior, accorded us the freedom of their departments. They also flung wide open the doors of their homes, in which we passed many an hour of happy, informal talk. Kinder hostesses it is impossible to conceive, and we who were privileged to enjoy their hospitality will never forget how largely the success of the Scandinavian Tour was due to their welcome.

OBITUARY

H. H. McNABB

We regret to record the death of Dr. H. H. McNabb, M.D., which occurred at his home at Prestbury, Cheshire, last month at the age of 74 years.

Harry Horsman McNabb was born and received his early education in Bolton, later passing on to the University of Manchester, where he qualified M.B., Ch.B. in 1898, taking the M.D. four years later. After a short period in general practice, he was appointed a resident at the Manchester Royal Eye Hospital and subsequently Assistant Honorary Surgeon, full Surgeon, Consulting Surgeon and Vice-President, his connection with the Hospital covering a period of 49 years. During most of this time he conducted an extensive

private practice, and his services were much in demand as a medico-legal expert witness. He was an active member (and ex-President) of the North of England Ophthalmological Society and an enthusiast at the Oxford Ophthalmological Congress, which he attended regularly.

In spite of a busy, and at times overburdened, professional life, McNabb had varied hobbies. In his younger days he was a keen cricketer, and continued to take a great interest in the game, even when he ceased to participate actively in it. He was an expert fisherman, was something of an authority on roses, a keen bridge player, and, before the last war, travelled considerably abroad. The writer remembers dining with him one night, and on his table was a set of dinner mats—ink on white silk—of the old halls of Cheshire, most beautifully drawn by him; craftsmanship of the highest order.

Never physically robust, his health broke down in his early forties, when he developed an active tuberculous chest lesion. He made an excellent recovery, but of necessity he lived subsequently a more limited life, which at times must have proved irksome, though he never complained of his ill-fortune. His last illness began some eighteen months ago, though mercifully he was saved a long period of pain and sueffring.

To his many friends, his colleagues and his patients, the keynote of his character was his gentleness and kindness. Never ruffled, never cross, always considerate and always willing to help a colleague—particularly a junior one—and to encourage his progress. As a clinical ophthalmologist he was in the front rank: a keen observer, an astute diagnostician, and so often in a difficult case able "to pull something extra out of the bag." His colleagues, who were fortunate to see his work, will perhaps remember most his superb operative ability. His fingers and his touch were perfect. It must be remembered that a great part of his operative life was spent in the days before the advantages of modern local anaesthesia were developed, and when the preparation of a patient consisted solely in the local instillation of a few drops of cocaine. In the ordinary sense he never seemed to operate on an eye—his fingers were so delicate and his touch so perfect. Even in those early days his patients were rarely restless, for he conveyed to them not only confidence but something of his own gentleness of character. It is a misfortune that no film of his operative work exists, for had it been so, it would have gone down to posterity as the perfection of our operative art. His colleagues will miss him sadly, but will remember him with affection and respect.

To his widow and his surviving son we offer our deepest sympathy.

O. M. D.

H. H. McNABB.

JOHN ROBERT FOSTER

BORN in Sleights, Yorkshire, in 1868. John Robert Foster qualified at Edinburgh in 1893. After holding House appointments at the Central London and Royal Westminster Ophthalmic and at the Golden Square Nose and Throat Hospitals, he was appointed as Ophthalmic Surgeon at the Hartlepools Hospital. A year later he was appointed as Ophthalmic Surgeon to the Cameron and Howbeck House Hospitals and the Hartlepools Education Authority as Aural and Ophthalmic Surgeon. He served in this capacity, being an excellent and careful surgeon, until at the age of 64 he had to retire from hospital and private practice owing to ill-health. His death occurred suddenly at the age of 81, at Danby, on August 5, 1949. He is survived by a widow and three children, the eldest of whom is Ophthalmic Surgeon to the General Infirmary at Leeds.

J. F.

FRIEDRICH P. FISCHER

THE death of Friedrich P. Fischer on July 23, 1949, at the age of 52, robs ophthalmology of one of its outstanding research workers. Fischer's interest lay mainly in the basic sciences, particularly in physical chemistry. Much of his earlier work was summarised in his remarkable contribution on The Water Content of the Eye, published in *Documenta Ophthalmologica* in 1938. The bearing of this highly abstruse work on glaucoma and on retinal detachment is obvious, and though Fischer could give no final answer, the work he has done is a permanent contribution to an exceptionally difficult subject. An equally important contribution bearing on the same clinical problems is represented by his recent paper on The Mechanical Properties of the Eye and its Tissues. His investigations on mycellia have a direct bearing on detachment, whilst his studies on elasticity and rigidity may ultimately help to clarify the problems of glaucoma.

Fischer's professional career was twice interrupted by the emergence of the Nazi horror. After 1933 there was no room for Fischer and his like in a Germany where all civilised values had collapsed. Through the wisdom of Professor Weve, Fischer found a congenial home at the Clinic at Utrecht. When he went to Utrecht at the age of 36 he took with him an international reputation in his own sphere based on over 40 publications, and his subsequent industry brought lustre even to the Utrecht Clinic with its great traditions. The occupation of Holland by the Nazis in 1940 interrupted Fischer's career for a full five years. With the

help of the highly organised Dutch resistance movement, and several false passports, he managed to elude the Gestapo, learning in the process how to trap rabbits in the woods, and to subsist on stolen chickens and stream-water. In the four years that were left to him at the end of the war he returned with renewed enthusiasm to his single-hearted devotion to research. A man of wide culture, he contributed to the study of the history of ophthalmology, as shown by his excellent paper on Goethe. He became one of the editors, and the leading spirit, of the revived *Documenta Ophthalmologica* and of the ophthalmic volumes in *Tabulae Biologicae.* In his work he was greatly assisted by his wife and his colleague, Dr. H. von Bunau. To her and to their two daughters goes out the sympathy of the profession at large.

A. S.

NOTES

International Exchange of Publications

A MANUAL on the International Exchange of Publications will be published this year by Unesco Clearing House for Publications, 19, Avenue Kléber, Paris 16e. Annexed to this manual will be a classified list of institutions willing to exchange their own publications, or publications regularly at their disposal. Relevant details, which should reach Unesco by October 1, 1949. are (a) name and address of institution (*e.g.*, library, university, learned society) ; (b) titles of publications offered ; (c) any special conditions of exchange.

* * * *

University of Toronto

THE Professor of Ophthalmology, Faculty of Medicine, University of Toronto, announces a 3-year post-graduate course in ophthalmology. Appointments are made in December, and work begins on the following July 1. A successful candidate is granted a special Fellowship worth approximately $1400, which enables him to devote the first year to one of the basic sciences of ophthalmology. He spends the other two years on the intern service of one or more of the University teaching hospitals, but must attend courses of instruction by members of the staff. Such teaching occupies about four hours a week from October to May, and the fee payable is $50 a year. Senior interns are taught how to prepare and deliver scientific papers.

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COMMUNICATIONS

STUDIES ON THE INTRA-OCULAR FLUIDS
Part 4 — The Dialysation of Aqueous Humour against Plasma*

BY

SIR STEWART DUKE-ELDER, HUGH DAVSON and D. M. MAURICE

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THERE have been many attempts over the last quarter of a century to determine whether the aqueous humour and the blood plasma were in thermo-dynamical equilibrium. One of the most direct ways of determining whether or not this is so is to dialyse the one fluid against the other across a separating membrane; if there is a migration of substances across the membrane, it is obvious that such an equilibrium does not exist. In previous work of one of us (Duke-Elder, 1927) using pooled aqueous humour of

* Received for publication, March 14, 1949.

several animals, it was found that such a transfer was not of great dimensions; but the present experiments, carried out in much more efficiently controlled conditions, demonstrate that a transfer from the aqueous humour into the blood-plasma is consistently found.

METHODS

General.—Dogs and cats were anaesthetised with nembutal; aqueous humour was removed from both eyes with a gauge 1 needle and syringe; blood was obtained by heart-puncture, heparinised, and equilibrated with alveolar air at body temperature; the plasma was separated by centrifugation in a corked tube. For studies on the chloride content and on conductivity, the fluids from a single animal were sufficient for an experiment; for studies on the distribution of sodium, the fluids from three animals were pooled in strict proportion.

Dialysis.—In Experiments Nos. 1-12, the plasma was placed in a collodion sac, prepared as described by Dale and Evans (1920), tied to the end of a piece of capillary tubing (Fig. 1), which was then sealed with sealing-wax. The sac was washed with a few drops of aqueous humour and then immersed in sufficient of

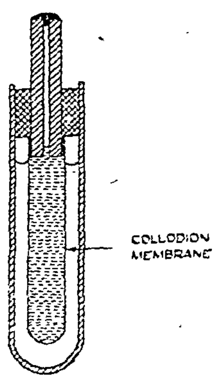

FIG. 1.

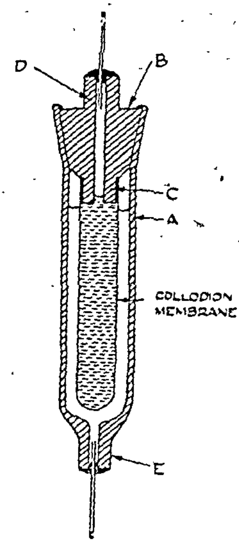

FIG. 2.

Dialysation apparatus

this fluid to cover it. A collar of rubber tubing round the capillary permitted the sac to stand in the fluid without touching the sides or bottom of the container. Evaporation was reduced (but apparently not always completely prevented) by covering the collar with paraffin-wax. The system was allowed to stand for about 16 hours at room temperature together with samples of the original fluids in stoppered tubes. During the course of the work it became evident that, in some of the experiments, evaporation of the fluids was taking place in the dialysing system; consequently the apparatus illustrated in Fig. 2 was devised. It consisted of an outer glass container, A, into which fitted a ground stopper, B. The base

of the stopper formed a slightly tapered projection, C, which was pushed into the top of the collodion sac, the junction being sealed with cellulose acetate paint. The stopper and the bottom of the container were pierced by holes, into each of which was sealed by sealing wax a length of glass tubing drawn out to capillary thinness. The stopper with its attached collodion membrane was placed in the container and fixed in position by wax or paint spread on the outside junction. An outer projection on the stopper, D, was pushed into a hole in a rubber bung; into the other end of this hole was pushed a glass tube joined to a length of rubber tubing so that by sucking or blowing on to this tubing the collodion sac could be collapsed or blown out. To fill the chamber, the sac was blown out, the bottom capillary placed under the required solution which was then drawn in by suction until the sac was completely collapsed. The chamber was then removed from the bung, inverted, and another similar projection, E, on the bottom of the container pushed into the hole. The sac was then filled with the other solution, normally plasma, by sucking it in through the capillary in the stopper. Some suction was maintained on the tube until the tip of this capillary was sealed with wax. The container was then removed from the bung and the other capillary likewise sealed.

By this means equal volumes of fluid were obtained inside and outside the sac. The sac was 8 mm. in diameter and the inside of the container about 11 mm. so that if the sac were cut so that it almost touched the bottom of the container, the fluid levels inside and outside were about the same. For the experiments described here two chambers were constructed to take 1 ml. or 2 ml. of solution inside the sac, but it is not of course necessary, although desirable, that the chamber should be completely filled either inside the sac or outside.

Stirring was achieved by fixing the chamber on a large pulley rotating at about 1 rev./sec.; at this speed the air bubbles in the compartments moved through the whole column of liquid and back during each cycle. Preliminary studies showed that equilibrium was established in about 30 min. but generally two to three hours were allowed.

To empty the sac the tips of the capillaries were broken off and the filling procedure followed in reverse. Even with the operations required in the repeated washing of the sac before filling, it should remain serviceable for at least half a dozen dialysations; it must, of course, be kept wet when not in use.

Chemical.—Sodium was determined by the Barber-Kolthoff (1928) technique on triplicate 0·5 ml. samples of the fluids, ashed as described in an earlier paper (Davson, 1939); the mean standard error of the thirty-four triplicate determinations was one part in 730; since the effects described in this paper involve changes of as much as one to two per cent. there is no doubt of their statistical significance. Chloride was determined on 0·2 ml. samples by the Sendroy technique (1937), the mean standard error of triplicate determination being one part in 300.

Dry weight.—About 1 ml. of plasma was evaporated to dryness on a sand-bath and heated for about 24 hours in an oven at 105°.

Conductivity.—The conductivity cell was in the form of a pipette of 0·3 ml. capacity with a flattened bulb into which were sealed two platinum wire electrodes, blackened in the usual manner. Connection to the bridge was made by two copper wires, soldered on to the electrodes and carried round the stem of the pipette. The junctions and leads were protected with a coating of wax and lacquer. The bulb was filled by suction through a rubber tube which was then clipped off and the tip of the pipette was sealed with a length of blocked cycle-valve tubing. The cell was immersed in melting ice contained in a Dewar flask. Before filling with a sample the cell could either be washed with distilled water and dried with alcohol and ether, or merely washed out with a fluid of conductivity close to that expected in the sample. The resistances were measured on a bridge constructed of normal radio components and calibrated with a decade resistance box. Duplicate readings on plasma or aqueous humour samples agreed to one part in a thousand.

pH.—The measurements were made with a glass-electrode reading against a calomel $\frac{1}{2}$ cell on a direct reading valve millivoltmeter. Alternate readings were taken of dialysed and undialysed fluids which were transferred as directly as possible to the measuring cell so as to avoid significant CO_2 loss.

RESULTS

Chloride.—The results with chloride on dogs are quite definite (Table I); as a result of a decrease in the original concentration of chloride in the aqueous humour (A_1), and of a rise in the corresponding concentration in the plasma (P_2), the ratio, R_{Cl}, changes from a mean value of 0·91 to one of 0·98. The two fluids are quite clearly not in equilibrium with respect to chloride. In cats the effects are not so large; nevertheless there is a definite

TABLE I

THE MOVEMENT OF CHLORIDES

The change in the Gibbs-Donnan ratio, R_{Cl}, following dialysis of plasma against aqueous humour. Expts. 21 to 24 refer to cats, the remainder to dogs. Expts. 1 to 16 were done with the earlier, 17 to 24 with the improved type of apparatus. A and P are the concentrations of chloride, in millimoles per kg. of water, in aqueous humour and plasma respectively. The suffices (1) and (2) refer to the figures obtained before and after dialysis respectively.

Expt.	A_1	P_1	R_1	A_2	P_2	R_2	$R_2 - R_1$
Dog 1	138.4	121.2	0.875	130.3	126.0	0.965	+ .09
2	145.4	130.0	0.895	140.1	134.6	0.96	+ .065
3	142.2	127.1	0.895	133.1	133.2	1.000	+ .105
4	134.5	123.9	0.92	129.0	129.9	1.007	+ .087
5	127.7	119.2	0.935	125.0	122.0	0.975	+ .04
6	131.7	123.0	0.935	132.1	128.5	0.975	+ .04
7	130.2	123.8	0.95	131.3	130.7	0.995	+ .045
17	128.0	118.2	0.923	126.9	123.0	0.97	+ .047
18	123.2	114.4	0.93	122.1	118.5	0.972	+ .042
19	129.9	115.9	0.893	121.6	122.4	1.005	+ .112
20	127.5	109.9	0 865	122.5	115.2	0.94	+ .075
Mean			0.911			0.979	
Cat 21	131.6	122.7	0.932	127.5	126.0	0.99	+ .058
22	127.5	123.9	0.973	128.9	124.6	0.968	— .005
23	130.6	119.1	0.91	129.5	123.4	0.953	+ 043
24	132.3	127.7	0.965	132.0	128.4	0.973	+ .C08
Mean			0.945			0.971	

change in the ratio following dialysis when this is low in the original fluids, but it would appear that in some animals the fluids are in equilibrium in respect to chloride whilst in others they are not. It will be noted that the decrease in concentration in the aqueous humour does not always equal the increase in plasma concentration, for the rise in concentration in the plasma was on occasions larger than the fall in the aqueous humour.

Sodium.—Some results with this ion are shown in Table II; they are equally consistent but not so striking in magnitude. The average value of R_{Na} changes from 1·036 to 1·057 in the dog,

TABLE II

THE MOVEMENT OF SODIUM

The change in the Gibbs-Donnan ratio, R_{Na}, following dialysis of plasma against aqueous humour. Expts 12, 13 and 15 refer to cats, the remainder to dogs. Pooled specimens from three animals used in each experiment. A and P are the concentrations of sodium, in millimoles per kg. of water, in aqueous humour and plasma respectively. The suffices (1) and (2) refer to the figures obtained before and after dialysis respectively.

Expt.	A_1	P_1	R_1	A_2	P_2	R_2	$R_2 - R_1$
Dog 8	150.4	154.6	1.027	146.6	155.6	1.062	+ .035
9	150.3	155.0	1.032	147.4	154.7	1.050	+ .018
10	149.8	157.2	1.050	149.1	160.5	1.077	+ .027
11	148.5	155.8	1.049	149.1	158.7	1.064	+ .015
14	149.8	154.0	1.028	148.5	154.1	1.038	+ .01
16	147.4	152.1	1.032	145.7	152.8	1.049	+ .017
Mean			1.036			1.057	
Cat 12	155.8	160.2	1.028	156.6	166.9	1.066	+ .038
	155.8	160.2	1.028	158.5	168.2	1.061	+ .033
13	152.3	160.8	1.056	150.3	161.2	1.073	+ .016
15	152.1	158.7	1.043	149.3	159.3	1.067	+ .024
Mean			1.042			1.068	

and from 1·042 to 1·068 in the cat. Once again we find that the change in aqueous humour concentration is not always balanced by that in the plasma.

In Experiments 8 and 9 the sac had been maintained in distilled water before use; this produced a diluting effect on the system which obscured the rise in plasma concentration; in all succeeding experiments the sac was equilibrated with saline; there was, however, evidence of evaporation, an effect which tended to obscure the fall in concentration of the aqueous humour (Experiments 10-12). This is well brought out by Experiment 12; in this experiment sufficient fluids were obtained for two successive dialyses, and as a result of the first dialysis the value of R_{Na} rose from 1·028 to 1·066. New lots of the same fluids were then placed inside and outside the sac and the system left for another 16 hours; it will be seen that the value of R_{Na} did not differ significantly from that obtained after the first dialysis, but that as a result of evaporation the concentrations of sodium in aqueous humour and plasma both rose. In the later experiments (Nos. 13 to 16) evaporation was excluded by the use of the new type of chamber; R_{Na} invariably increased as a result of dialysis as before, but even under these conditions the loss in concentration in the aqueous humour was not entirely accounted for by a rise in the plasma concentration. It is not easy to explain

these discrepancies. It is possible that the collodion membrane itself is not in equilibrium with the fluids surrounding it; it may tend to turgesce, to adsorb or desorb ions, the particular effect observed depending on its previous history. In view of the large number of animals required and the extreme laboriousness of the chemical technique, it was not thought worthwhile investigating the point further; all ten dialyses, representing the fluid from 27 animals, concurred in showing that the ratio R_{Na} increased as a result of dialysis; dilution or concentration of the system by a few per cent. should produce slight errors in the ratio, but too small to be detected (cf. for example Expt. 12).

Conductivity.—The changes in conductivity are shown in Table III. In all cases there was an increase in the resistance of the aqueous humour and a decrease in that of the plasma, *i.e.*, the changes were such as could be produced by a movement of sodium

TABLE III

CONDUCTIVITY EXPERIMENTS

Changes in electrical resistance of plasma (ΔR_{Pl}) and aqueous humour (ΔR_{Aq}) as a result of dialysis. Expts. 25 to 33 on cats; Expt. 34 on a dog. In Expts. 30 and 32, whole blood was placed in the sac instead of plasma.

Expt.	ΔR_{Aq}	ΔR_{Pl}	$\frac{\Delta R_{Pl}}{\Delta R_{Aq}}$
Cat 25	1.7	−3.6	2.1
26	2.5	−8.7	3.5
27	0.6	−0.7	1.2
28	1.8	−2.1	1.2
29	1.0	−1.8	1.8
30	1.2	−2.6	1.45
31	7.3	−10.6	1.45
32	0.5	−1.7	2.4
33	0.1	−1.2	2.0
Dog 34	6.5	−4.3	1.5
Mean	2.2	−3.7	1.7

and chloride from the aqueous humour into the plasma. It may be computed, from the characteristics of the dialysis system, that the ratio: *Decrease in Resistance of Plasma/Increase in Resistance of Aqueous Humour* should be in the region of 1·4; the mean ratio is 1·7.

pH.—The increase in the value of R_{Na} might conceivably be due to an alkalinity of the dialysis system resulting from the loss of CO_2; the observed changes, however, would require an increase of about 50 per cent. in the base-binding power of the plasma, a change that could be achieved only by a change of pH in the region of one unit. It was not feasible to make pH measurements on the fluids used for analysis; separate dialysis

experiments were therefore carried out with both types of sac to determine whether any significant change in the pH of the two fluids took place as a result of the dialysis. It was found, in general, that the pH of the plasma was unaffected by dialysis whilst the aqueous humour tended to become more acid; presumably this is because the losses of CO_2 in the manipulation cause the aqueous humour to become alkaline; dialysis with the better buffered plasma tends to restore the pH to the physiological range.

The re-formed aqueous humour.—Earlier work (Davson and Weld, 1941) has shown that the aqueous humour re-formed after paracentesis is in close approximation to equilibrium with plasma

TABLE IV

THE SODIUM DISTRIBUTION IN PLASMOID AQUEOUS HUMOUR

The Gibbs-Donnan ratio, R_{Na}, in the re-formed aqueous humour. R_1 and R_2 are the ratios obtained with the normal aqueous humour before and after dialysis respectively; R_3 is the ratio obtained with normal plasma and re-formed aqueous humour.

Expt.	R_1	R_2	R_3	Protein in Re-formed Aqueous Humour
9	1.032	1.050	1.012	—
10	1.050	1.077	1.010	3 per cent.
11	1.049	1.064	1.024	2.5 per cent.
12	1.028	1.064	1.011	3 per cent

in respect to chloride: in the present work the fluid, re-formed within about half an hour of withdrawal of the normal aqueous humour, was analysed for sodium; the results are shown in Table IV. It will be observed that R_{Na} has become quite close to unity.

DISCUSSION

The results of these experiments show that the aqueous humour is not in thermo-dynamic equilibrium with blood plasma in so far as the distribution of sodium and chloride between the two fluids is concerned, for these substances are both in excess in the aqueous humour and migrate from this fluid to the plasma on dialysation. It might be suggested that the high concentration of sodium in the aqueous humour could be accounted for on the basis of a difference of pH between plasma and aqueous humour resulting, for example, from the formation of lactic acid in the metabolism of the lens; but such an explanation, even if it were acceptable, could not account for the fact that the excess of

chloride in the dog's aqueous humour actually exceeds that of sodium. The fact that arterial blood-plasma was arbitrarily chosen as the reference fluid may give rise to question, but the concentrations of sodium in arterial and venous plasma are not appreciably different, so that it is unlikely that the concentration in the capillary plasma—the fluid with which the comparison should be made—differs measurably from that in the arterial plasma used. We are therefore forced to the conclusion, already arrived at in our earlier chemical work, that energy is expended in transferring sodium and chloride from the blood to the aqueous, that is, that a process of secretion exists.

In the dog, the deviation of the concentration of chloride from equilibrium was considerably greater than that of sodium, the excess of chloride in the aqueous humour amounting to about seven per cent. or some 9 millimoles per litre; since the discrepancy of sodium amounts to only about 3 millimoles per litre, the results suggest that some other cation is present in excess; studies on the distribution of potassium (Davson, Duke-Elder and Benham, 1936), calcium and magnesium (Stary and Winternitz, 1932) have not revealed excesses of these ions in the aqueous humour of a magnitude sufficient to account for the excess of chloride. Presumably an organic cation is present. In the cat the deviation of the chloride ratio from the equilibrium value was considerably smaller, and on occasions it was found that the chloride ion was actually at equilibrium; in this respect, therefore, there seems to be a significant quantitative difference in physiology between the cat and dog.

The plasmoid aqueous humour formed after paracentesis is an entirely different case. It is seen that the ratio for the concentration of sodium (R_{Na}) as seen in Table IV approximates unity and this is most simply interpreted as indicating that during the rapid process of filtration associated with the re-filling of the anterior chamber, the diffusible ions filter through the blood-aqueous barrier in amounts proportional to their concentrations in the plasma. There is thus no attempt initially to form a Donnan equilibrium: only at a later stage would the resultant potential impose a different ionic distribution. This, of course, is in accord with the view that in the conditions of stress resulting from the collapse of compensatory pressure on the outer side of the capillary walls, the normal blood-aqueous barrier is disrupted and direct transference takes place through widely opened spaces between the endothelial cells so that a direct transudation of substances—and sometimes of whole blood—takes place.

SUMMARY

Direct dialysation of the aqueous humour against the blood plasma shows by chemical analyses and conductivity measurements that there is a transference of sodium and chloride from the former to the latter. The two fluids are therefore not in

equilibrium and in respect to sodium and chloride secretory energy must be postulated in the formation of the intra-ocular fluid.

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AN INVESTIGATION INTO THE MODE OF HEREDITY OF CONGENITAL AND JUVENILE CATARACTS*

BY

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NORWAY

IT has been generally accepted since the investigations of Nettleship (1905) and Bateson (1909), that congenital and juvenile cataracts are inherited as dominant characteristics. It is reasonable that this should be so, for the literature provides many examples of cases in which such cataracts have been traced through several generations, and it leaves no doubt about the existence of dominant types.

There are, however, many reported cases of congenital and juvenile cataracts appearing sporadically, or in small numbers within the same family, and in which they have not been traced to succeeding generations. Such cataracts are frequently recorded as "familial"; they are often of the congenital or juvenile variety, and the possibility of their hereditary nature has received little consideration.

Franceschetti (1930) makes the following statement in Kurzes Handbuch der Ophthalmologie: "Das häufige isolierte Auftreten bei Geschwistern liesse auch an recessive Vererbung denken. Da aber Konsanguinität selten ist, kommt unregelmässige Dominanz in Frage."

Waardenburg (1932) says: "Auch die angeborene Katarakt wird im allgemeinen in dominanter Weise vererbt. Es liegen aber

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einige Beobachtungen vor, wodurch die Möglichkeit, dass es vielleicht eine rezessiv-erbliche Typen gibt, nicht ganz in Abrede gestellt werden kann. Die Rolle der Blutverwandtschaft ist eine geringe."

In "Handbuch der Erbkrankheitan" (1938), Bücklers has given the following declaration: "Das Schriftum ist zwar reich an Mitteilungen über erbliche Stare, doch sind viele Veröffentlichungen nicht zu verwerten, weil ausführliche Beschreibungen und gute Abbildungen fehlen. Es soll deshalb nicht verschwiegen werden, dass unsdr Wissen gerade auf diesem Gebiete noch lückenhaft ist."

Emphasis has been placed on the rôle of exogenous factors, *e.g.*, spasmophilia and rickets in the aetiology of just these types of cataract, and more recently attention has been drawn to the influence of virus diseases, *e.g.*, rubella. The possibility of hereditary influences tends to be overlooked and calls for further investigation.

With this possibility in view, all cases of congenital cataracts and juvenile cataracts which came under the author's care during six years as eye-specialist in *Telemark*, Norway, have been re-examined. This country district is relatively isolated and intermarriage is frequent, so that grouping of recessive genes is to be expected, with a correspondingly high number of homozygotes. Although statistical proof is lacking, hereditary eye diseases appear to be very common in this district.

Patients with congenital and juvenile cataracts were examined. In the published pedigrees the individuals physically examined are marked thus ◎. Information about their families was acquired from the patients themselves, their parents, their physicians, from parochial registers, and in some cases from other clinics.

The following are the more important points in the history of each patient:

Number of children in the family; number of affected individuals and their sex; convulsions or rickets in childhood; rubella or other diseases of the mother during pregnancy; consanguinity of the parents.

In the examination of the patient, the following points received attention:—

Type of cataract; comparison with types of cataract in affected siblings; uni- or bilateral; association with other defects or eye diseases, *e.g.*, nystagmus, microcornea; prognosis of the cataract.

The main object of this paper is to investigate the mode of inheritance in the reported cases of congenital and juvenile cataracts.

MATERIAL

(a) Survey

Within 17 families, 27 cases of congenital and juvenile cataracts are reported, 20 as congenital and 7 as juvenile cataracts.

In 8 sibships the cataract was evident in 2 or more individuals. In 7 sibships consisting of more than 2 individuals, only 1 was affected. In 2 cases the affected person was the only child.

Among the 27 affected individuals, 14 were males and 13 females. In 9 of the 17 families the parents of the affected individuals were related, and in 5 of these the parents were first cousins. In 4 families the relationship was more distant.

As to the diagnosis, 20 cases are recorded as congenital cataracts, with different sub-titles — cat. totalis, subtotalis, nuclearis, membranacea, polaris posterior et polaris anterior. In 7 of the patients the diagnosis is cat. juvenilis, with the sub-titles of cat. corticalis posterior in 1 (Case 15) and cat. zonularis in the other 6. Possibly some of these zonular cataracts were, in fact, also congenital.

The cataracts were bilateral in all cases, except in Case No. 7. In Case No. 5 the cataract was unilateral at birth, but appeared later in the other eye.

Within 7 of these families (Nos. 1, 4, 5, 8, 12, 14 and 17) cases of cataracta senilis were also found, but only in 1 family (No. 12) was the senile cataract recorded in the father of patients with congenital cataract. In the rest, the senile cataracts were spread over other generations or within other side-branches.

Two of the patients (Cases Nos. 12 and 13) also suffered from retinitis pigmentosa, as well as cataracta corticalis posterior and polaris anterior, and in Case No. 13 surdo-mutitas was also found. One of the patients (No. 14) was feeble-minded.

In 2 of the patients (Nos. 22 and 23) there was a history of convulsions and rickets in childhood. Case No. 23 also had enamel defects of the teeth.

None of the patients' mothers could remember having had rubella or other infectious diseases during pregnancy.

Case Reports and Family Histories

Family 1: *Cases* 1 *and* 2.

O.S., male, born November 12, 1927, and A.S., male, born August 12, 1942, are No. 1 and 3 in a fraternity of three. Born in Bö, Telemark.

Case 1, *O.S.*, male. The cataract was noticed before the age of one year. Operation performed at age of 3 years in the right eye and at age of 3½ years in the left eye. A homogeneous greyish opacity covered all the pupillary area (3 mm. in diam.). No red reflex. Later on he was again admitted to a clinic for discissio cataractae o.u.

9*years old*: No nystagmus. Corneal diameter normal o.u. Visual acuity o.d. + 13 = 5/15; o.s. + 13 = 5/30. Cat. sec. o.u. The patient had always been

healthy. No convulsions. No indications of rickets. His mother was healthy during pregnancy.

Diagnosis: Cataracta congenita (subtotalis).

Case 2, A.S., male. The patient's parents noticed the cataract immediately after birth. Otherwise he had been in good health. No convulsions. No indications of rickets. Mother healthy during pregnancy. Examined at age of 18 months and admitted to a clinic at age of 3 years.

3 years old: The patient was well-built and looked well. No sign of rickets. In both eyes there was an opacity in the central part of the lens and also considerable opacities in cortex. Discissio cataractae o.u.

5 years old: Repeated needlings. Vision: o.d. + 10 = 5/20; o.s. + 10 = 5/20.

Diagnosis: Cataracta congenita (subtotalis).

Pedigree information. See Fig. 1. The family was traced through four generations. In a fraternity of three (gen. IV) No. 1 and 3 had congenital cataract. No. 2, G.S., female, was normal (16 years old). The parents (G.S., male, 58 years, and

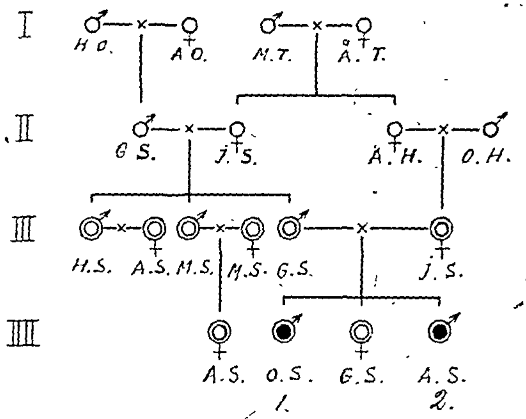

FIG. 1.

Family 1. Pedigree demonstrating that the parents of Case I, O.S., male, and Case II, A. S., male, both with congenital cataracts, were first cousins, H.O. (gen. I) aged 76, and H. S. (gen. III) aged 64, had senile cataracts.

I.S., *female, 47 years) of the affected children were normal.* G.S., male, was No. 3 in a fraternity of three. No. 1, H.S., male, 64 years old, had a cat. senil. incip. with sector-shaped opacities in the anterior cortex. Vision: o.d. = 5/15; o.s. = 5/20. No. 2, M.S., male, 61 years old, his wife M.S., 62 years old, and their daughter, A.S., 17 years old, were all normal.

The grandparents of the affected children (O.S., T.S., A.H. and O.H., gen. II) all died at an advanced age (69, 79, 59 and 83 years) and had had good vision. Their great grandparents (M.T. and A.T., gen. I) died aged 45 and 34 years respectively, and had had good vision. The paternal great-grandfather (H.O., gen. I) had cat. senil. and died at the age of 76 years.

From the pedigree it is seen, that the patient's parents were first cousins.

Summing up, there were in this family two cases of cat. congen. The patient's parents were first cousins. Furthermore there were two cases of cat. senil. one in the patient's uncle and one in their great grandfather.

Family 2: Case 3.

M.Đ., female, born May 12 in Skien, and was No. 1 among two sisters.

Case 3, M.D., female. History given by the parents of a healthy childhood. She had never had spasms or rickets. The cataract was noticed when 1 year old.

2 years old: Referred to a clinic for operation. At that time o.d.: Dense greyish

opacity in the pupillary area. No red reflex. O.s.: Grey opacity in the pupillary area with no shadow of the iris. She was operated on several times o.u. Attended elementary school and was able to read with the left eye. The right was almost blind. The patient's mother was said to have been healthy during pregnancy.

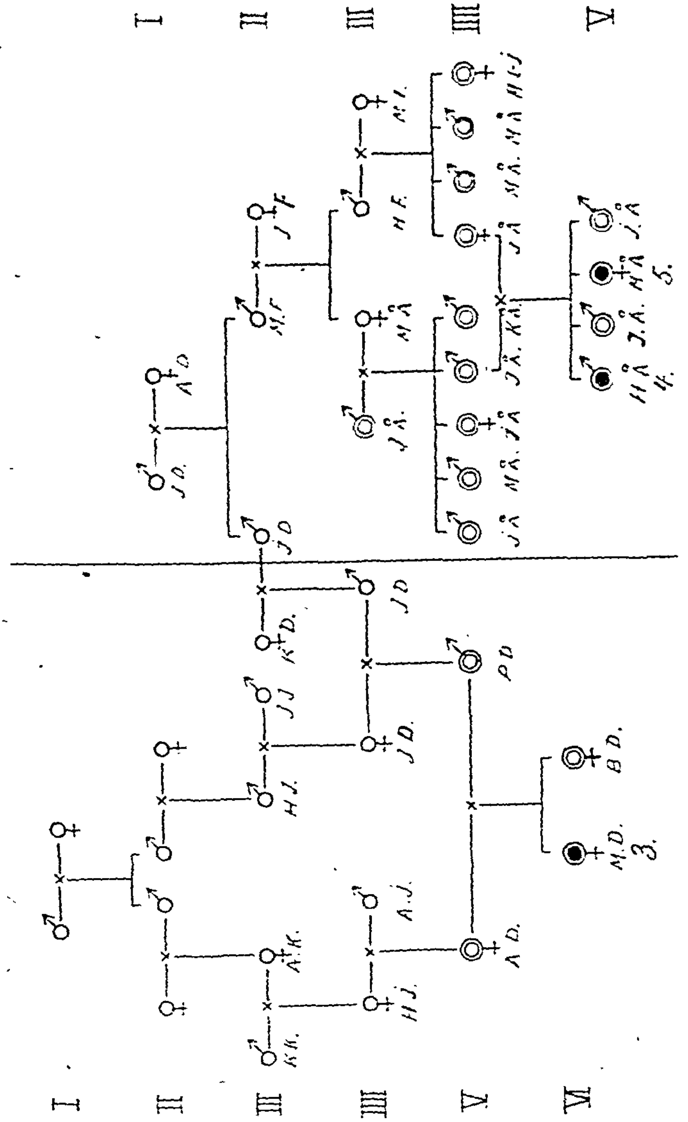

FIG. 2.

Family 2. Pedigree demonstrating that the parents of Case 3, M. D., female, with congenital cataract were third cousins. The consanguinity between the families 2 and 3 is also demonstrated.

FIG. 3.

Family 3. Pedigree demonstrating that the parents of Case 4, H. A., male, and Case 5, M. A., female, both with congenital cataracts, were first cousins.

21 *years old*: Nystagmus. Corneal diameter normal o.u. o. dext. in divergens. Total coloboma. Cat. sec. o.s. Pupillary area clear. Good red reflex. Vision o.d. P.L., O.s.=5/10.

Diagnosis: Cataracta congenita (subtotalis).

Pedigree information. See Figs. 2 and 3. The family was traced through six

generations. The patient's sister (B.D., female, aged 22 years old) was normal. Their parents (A.D., female, aged 51 years, and P.D., male, aged 53 years old), were also normal. Their grand-parents (generation IV) died at the ages of 70, 39, 47 and 87 years, and had normal vision. Their great grand-parents (gen. III) died at the ages of 90, 90, 87 and 70 years, and had normal vision. Information about the other generations was negative except that No. 2 and 3 in gen. II were brothers, and that they had good vision. Both of them died at an advanced age. The pedigrees of No. 2 and 3 show that there is consanguinity between the two families.

Hence, in this family there was one case of cat. congenita (subtotalis) in a fraternity of two. The patient's parents were third cousins. There was consanguinity also between this family No. 2 and the family No. 3.

Family 3: *Cases* 4 *and* 5.

H.A., male, born February 20, 1920, and M.A., female, born June 2, 1922, in Siljan, Telemark, were No. 1 and 3 in a fraternity of four.

Case 4, *H.A.*, male. The cataract was noticed at the age of 6 months. No spasms. No rickets. Admitted to a clinic at the age of 3 years. His mother was healthy during pregnancy.

3 *years old*: It was impossible to identify the type of cataract from his record. Possibly it was a membraneous cataract. Operation on both eyes. At the ages of 4 and 5 years he was operated again, and was then able to read and passed intermediate school examinations.

17 *years old*: Nystagmus present. Corneal diameter normal o.u. Cat. sec. o.u. Vision o.d. + 8 = 5/20; o.s. + 8 = 5/20.

The patient was otherwise healthy and well developed for his age.

Diagnosis: Cataracta congenita (membranacea).

Case 5, *M.A.* The cataract was noticed immediately after birth. No spasms or rickets. Her mother healthy during pregnancy. Her right eye was operated on at the age of 2 years. Had good vision in left eye. Also in this patient it was impossible to state the type of the cataract from the description, but most probably it was a total cataract.

24 *years*: Looked healthy. No nystagmus. Corneal diameter normal. O. dext in divergens. The pupillary area was clear with red reflex. O. sin. Central opacity in posterior cortex. Vision o.d. Counts fingers at ½ m.; o.s. = 5/20. Operation still not advised in left eye, as reading was good.

Diagnosis: Cataracta congenita (totalis)?

Pedigree information. See Fig. 3.

Investigations through five generations. The patients were No. 1 and 3 in a fraternity of four. No. 2, J.A., male, born March 26, 1921, and No. 4, J.A., male, born July 30, 1923, were both normal. The patient's parents J.A., aged 56 years, and I.A., aged 55 years, were normal too. They were first cousins. The other members of the parents' group and their children were all normal. Three of the patient's grandparents (gen. III) died at advanced ages (72, 59, 82 years). No. 1, J.A., 92 years old, was still alive, and had normal eyes. Two of the patient's grandparents (M.A., female, and H.F.) were sister and brother. Their parents (gen. II) died aged 61 and 55 years, and had good vision. The connection between this pedigree and the previous one is obvious and demonstrates that the father of Case 3 (Fig. 2) was second cousin of the father and the mother of Cases 4 and 5 (Fig. 3). The side branches in the descendants after M.F. and I.F. (gen. II) were traced and no other cases of cataract found. In this family two patients of a fraternity of four had cat. congenita (?membranacea, totalis). The patient's parents were first cousins. Consanguinity between this family and the previous family No. 2 was noted.

Family 4: *Case* 6.

O.E., male, born August 26, 1939, in Rauland, Telemark, was No. 2 in a fraternity of two.

Case 6, *O.E.*, male. The cataract was noticed at the age of 1 year. His mother was healthy during pregnancy. He looked well. No spasms. No rickets.

1 *year old*: Nystagmus. Corneal diameter 9 mm. o.u.

In both of the lenses there were opacities, most dense in the central part, but also in cortex. Faint red reflex in the peripheral areas of the lenses.

5 years old: Mydriasis. o.u. The lenses were opaque all over, more dense in the central part than in the periphery. Faint red reflex from the lens-periphery. Vision: eyesight enough to walk by himself. The patient was operated on: Discissio et evacuatio cataractae o.u. Vision after operation difficult to state (+11=?5/20 o.u.).

Diagnosis: Cataracta congenita (totalis).

Pedigree information. See Fig. 4.

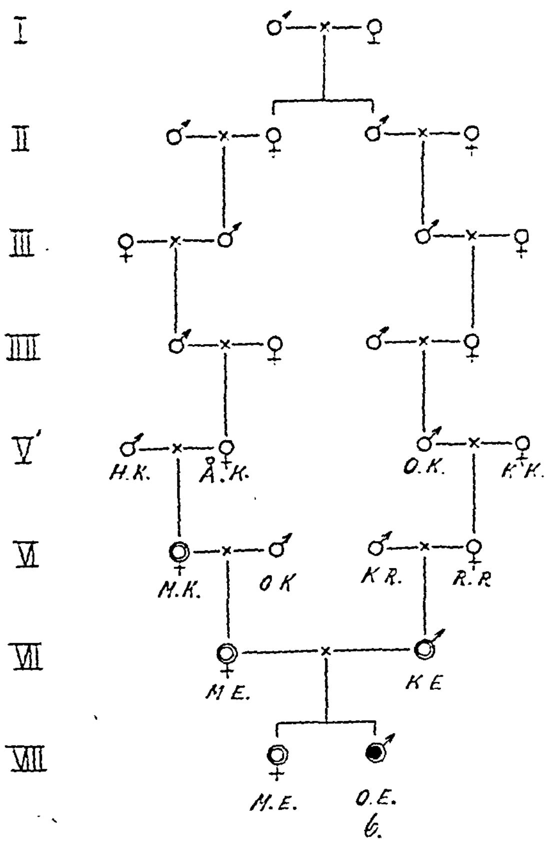

FIG. 4.

Family 4. Pedigree demonstrating that the parents of Case 6, O. E., male, with congenital cataract, were fifth cousins. O. K., gen. V, had senile cataract. (Aged 83).

The family was traced through eight generations. The patient's sister, M.E., was examined 18 years old, and was normal. His parents M.E., female, aged 49 years, and K.E., aged 68 years, were also normal. They were fifth cousins. The sisters and brothers of the patient's parents, and their children had normal eyes. The patient's grand-parents (gen. VI) of which only M.K., aged 78 years, was still alive, had good vision. Three of them died at advanced ages (70, 70 and 80 years old). From gen. V it was known that H.K., A.K., O.K. and K.K. died at advanced ages (81, 75, 83 and 90 years respectively) and, with the exception of O.K., who had cat. senilis, all had good vision. About the individuals in the other generations

I, II, III, and IV, it was only known that they died at advanced ages and probably had good vision. The descendency from gen. I was traced extensively, but no other cases of congenital or juvenile cataracts were found.

In this family, one patient in a fraternity of two had cat. congenita (totalis). The parents of the patient were fifth cousins. The patient's-great grandfather had cat. senilis.

Family 5: *Case* 7.

I.L., male, born 1943, was the only child. Born in Mo, Telemark.

Case 7, *I.L.*, male. His parents noticed the cataract at birth. No spasms. No rickets. His mother was healthy during pregnancy.

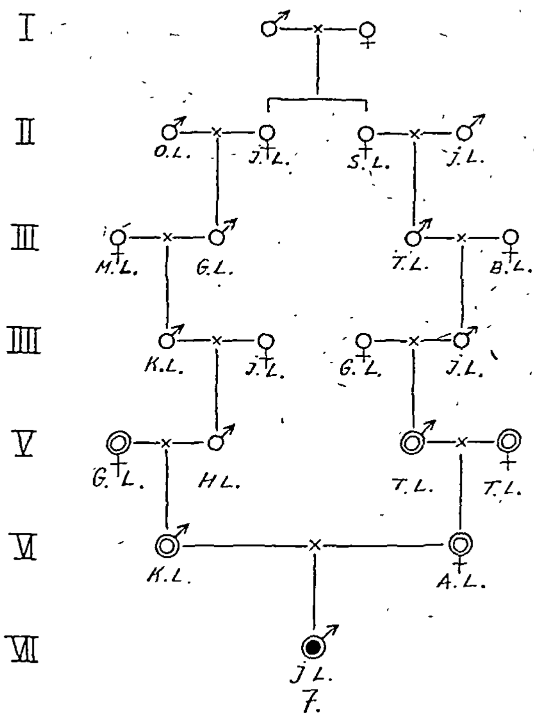

FIG. 5.

Family 5. Pedigree demonstrating that the parents of Case 7, J. L., male, with congenital cataract, were fourth cousins. G. L., gen. V, (aged 70), had senile cataract.

4 years old: The patient looked well. No nystagmus. Corneal-diameter normal o.u. *o.s.* In the central part of the lens there was a grey opacity formed as a disc. No riders. Red reflex around the opacity *o.d.* The lens was clear. Fundus normal. Vision: o.d.=C.F. at 1 m.: o.s.=5/5.

Diagnosis: Cat. congen. (nuclearis) o.d.

Pedigree information. See Fig. 5.

Investigations into the family was carried out through seven generations. The patient's parents, K.L., male, aged 43 years, and A.L., female, aged 32 years, were normal. They were fourth cousins. The other members of the parents' fraternities and their children were normal. The patient's grandparents (gen. V) were still alive H.L. excepted, who died aged 58 years, and had good vision. The others

were G.L., female, aged 70 years, T.L., male, aged 62 years, T.L., female, 78 years old. The first one had cat. senilis with wedge-shaped opacities in cortex. Vision: o.d. = 5/20, o.s. 5/15. The others had normal eyes. Information from the other generations disclosed no cases of cataract and these individuals died at advanced ages and were supposed to have had good vision. Investigations into their descendants disclosed no congenital or juvenile cataracts.

In this family, the only child of normal parents, who were fifth cousins, had cat. congen. (nuclearis). One of the grandmothers had senile cataract.

Family 6: Cases 8 and 9.

E.M., male, born May 31, 1901, and K.M., male, born June 28, 1905, in Mo, Telemark, were No. 1 and 3 in a fraternity of three.

Case 8, E.M., male. The cataract was noticed at birth. Had always been healthy. No spasms or rickets. Mother healthy during pregnancy.

9 years old: He looked healthy. Nystagmus was present. Corneal-diameter normal o.u. Nuclear opacity in the lens, with a less dense zone around this. Good red reflex peripherally, o.u. Was operated in both eyes at the ages of 9 and 10 years, and was then able to read. Died 21 years old.

Diagnosis: Cat. congenita (nuclearis).

Case 9, K.M., male. The cataract was noticed at birth. No spasms or rickets. Was 5 years old when admitted to a clinic. No disease in mother during pregnancy.

5 years old: Looked healthy. Nystagmus present. Corneal-diameter normal. In the pupillary area a greyish, 4 mm. diam. disc-like opacity. Red reflex peripherally. Probably a nuclear cataract o.u. Operated on both eyes. Vision o.d. + 11 = 6/36; o.s. + 11 = 6/36.

25 years old: In later years the vision had diminished. Glaucoma diagnosed o.d.

43 years old: Right eye became blind at the age of 26 years. Then glaucoma developed in the left eye. Vision: o.d. amaurosis: o.s. + 10 = 5/30. Intraocular tension o.s. 40 mm. Hg despite pilocarpine.

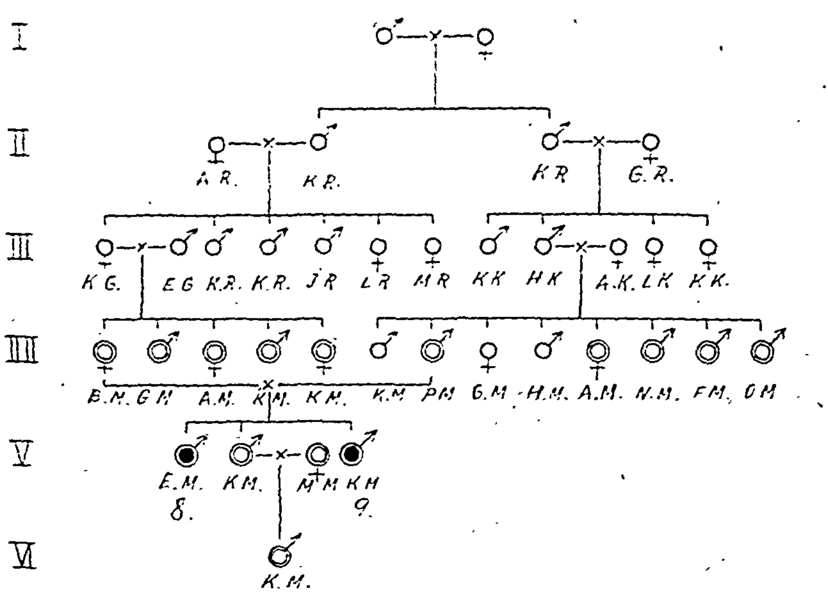

FIG. 6.

Family 6. Pedigree demonstrating that the parents of Case 8, E.M., male, and Case 9, K.M., male, both with congenital cataracts, were second cousins.

Diagnosis: Cat. congen. (nuclearis). Glaucoma.
Pedigree information. See Fig. 6.

Investigations through six generations were carried out. The patient's brother, K.M., aged 45 years, his wife, M.M., aged 28 years, and their child, K.M., 2 years old were normal. Their mother, B.M., aged 82 years, was No. 1 in a fraternity of five. All these and their children had normal eyes. The patient's father, P.M., aged 90 years, and No. 5, 6, 7 and 8 in his fraternity, and their children were all normal. No. 1, 3 and 4 of this fraternity died aged 86, 75 and 70 years old respectively, and had good vision. The paternal grandparents (gen. III) died aged 84 and 80 years, and had good vision. Three of their brothers and sisters died at an advanced age and had good eyesight. The maternal grandparents (gen. III), K.G. and E.G., died at the ages of 72 and 62 years and had good vision. In K.G.'s fraternity there were five other members who all died at advanced ages and had good eyesight. The patient's parents were second cousins.

In this family there were two cases of cat. congenita (nuclearis). The patient's parents were second cousins.

Family 7: *Cases* 10 *and* 11.

E.S., male, born 1885, and O.S., female, born 1889, in Siljan, Telemark, are No. 3 and 5 in a fraternity of nine.

Case 10, *E.S.*, male. He stated that he always had poor vision. Could read at school. His mother was healthy during pregnancy.

50 *years old*: He looked well and had always been healthy. No nystagmus. Corneal-diameter was normal o.u. O. dext.: In the central part of the anterior lens capsule there was a whitish opacity of 2·5 mm. diameter. In the posterior cortex there was a central rosette-like opacity of about 5 mm. diameter. Otherwise this lens was clear. O. sin.: The same picture. Fundus normal o.u. Vision: 5/20 o.u. No operation was advised, as ability to read was fair. He was drowned at age of 60 years.

Diagnosis: Cat. congenita (Cort. post. et pol. ant.).

Case 11, *O.S.* She always had poor vision, but was able to read at school. Vision diminished within the last years. Mother healthy during pregnancy.

50 *years old*: Enjoyed good health. No spasms or rickets. No nystagmus. Corneal-diameter normal.

O. dext. In the central part of the anterior lens capsule a whitish spot of 2 mm. diameter was seen. In the posterior cortex there was a central rosette-like opacity of 4 mm. diameter. In addition widespread powder-like opacities were seen in the lens. O. sin. similar picture. Fundus normal o.u. Vision=5/20 o.u.

59 *years old*: Vision diminished, at that time=5/30 o.u. Also wedge-like opacities noted in anterior cortex. Extractio cataractae o.d. After operation, vision=5/6.

Diagnosis: Cat. congen. (cort. post. et pol. ant.).
Pedigree investigation. See Fig. 7.

The pedigree was followed through five generations. The patient's siblings were: No. 1, H.N., female, aged 65 years old. Normal eyes. Her husband died 45 years old, and had good vision. Their five children between the ages of 22-46 years were all normal. No. 2, O.S., male, aged 62 years, was normal. No. 4, B.O., female, and her four children, aged 26-31 years, were normal. No. 6, N.S., male, died 41 years old, but had good vision. No. 7, J.S., male, 52 years old, his wife and their three children, aged 20-23 years, were all normal. No. 8, P.O., female, and her husband died 40 and 60 years old respectively, and had good vision. Their four children, aged 23-30 years had normal eyes. No. 9, H.H., female, aged 46 years old, her husband and their three children, aged 10-20 years, were all normal. The patient's parents N.O., male, and B.O., died aged 77 and 62 years old respectively, and had good vision. The father had three siblings who all died at advanced ages and had good vision. The mother had seven siblings who also died at advanced ages and had good eyesight. The patient's parents were first cousins. The patient's grandparents O.H., A.H., O.O., and E.O., died aged 89, 60, 70 and 80 years old respectively, and had good eyesight. (A.H. and O.O. were siblings.) The parents of the last mentioned (H.H., male, and J.H.) died aged 70 and 94 years old respectively, and had good vision.

The descendants from these were all traced as far as possible, but only the two recorded patients with cataract were found.

In this family two cases of [illegible] cataracts [illegible] among nine siblings were recorded. The patients' parents were first cousins.

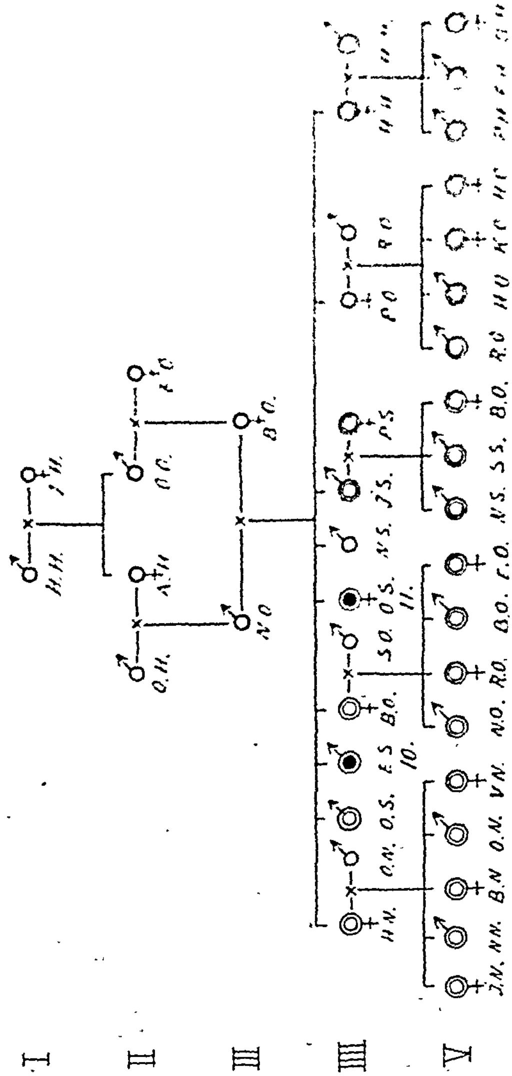

FIG. 7.

Family 7. Pedigree demonstrating that the parents of Case 10, E. S., male, and Case 11, O. S., female, both with congenital cataracts, were first cousins.

Family 8: *Case* 12.

K.K., male, born March 13, 1908, in Drangedal, Telemark, was No. 1 in a fraternity of five.

Case 12, *K.K.*, male. The patient was healthy during childhood. No spasms. No rickets. His eyesight had been poor as far back as he could remember. Difficulty in seeing in the darkness. His mother was healthy during pregnancy.

38 *years old*: General condition good. No nystagmus. Corneal-diameter normal o.u.

O. dext.: There was an anterior polar opacity of 2 mm. diameter in the lens. In the posterior cortex there was a rosette-like opacity. Otherwise the lens was clear. In the fundus retinitis pigmentosa was seen. O. sin.: Corresponding changes. Vision=5/20 o.u. Visual fields were constricted.

Diagnosis: Cat. congenita (Cort. post. et pol. ant.). Retinitis pigmentosa.

Pedigree information. See Fig. 8.

The pedigree information covered four generations. The patient's siblings were normal. They were aged 27-35 years. His parents O.K., male, aged 64 years, and A.K., who died 65 years of age of tuberculosis, were both examined, and had normal eyes. The patient's father was No. 1 in a fraternity of six. No. 2, I.K., female, was unmarried, and had normal eyes. No. 3, A.M., female, 57 years old, and her three children, aged 24-28 years, were all normal. No. 4, J.K., male, aged

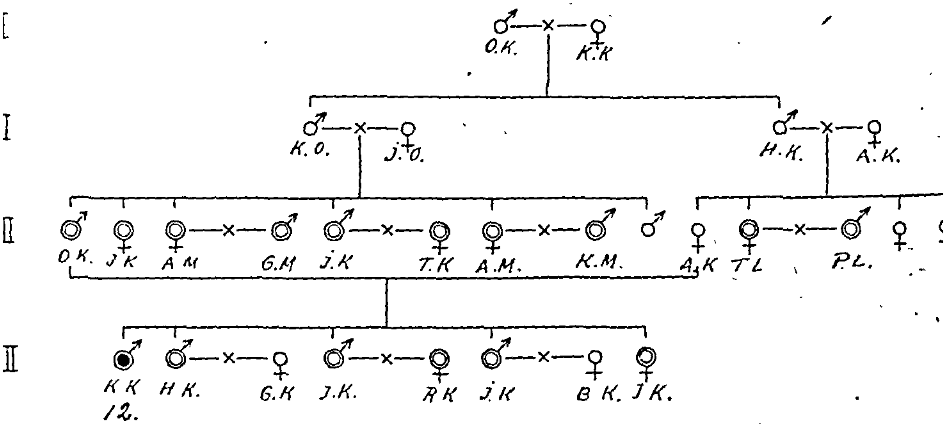

FIG. 8.

Family 8. Pedigree demonstrating that the parents of Case 12, K. K., male, with congenital cataract, were first cousins. K. O. (gen. II), aged 71, had senile cataract.

54 years, had one child, 16 years old. Both had normal eyes. No. 5, A.M., female, aged 51 years, and her two children, 30 and 28 years old, were all normal. No. 6 died 20 years old, and had at that time apparently normal eyes. The patient's parents were first cousins.

The patient's mother had a sister who was still alive, T.L., 65 years old, and she had normal eyes.

His paternal grandfather, K.O., died 71 years old, and had then a senile cataract (from his physician). The grandmother, I.O., died 70 years old, and had good eyesight. His maternal grandfather, H.K., and grandmother, A.K., died aged 72 and 70 years respectively; and had good vision. The patient's paternal and maternal grandfathers were brothers.

In this family, one among five siblings were found to be affected. Diagnosis: Cat. congenita (cort. post. et pol. ant.). Retinitis pigmentosa. The patient's paternal grandfather had cat. senil. His parents were first cousins.

Family 9: Case 13.

A.K., female, born 1911, in Kragero, Telemark, and was No. 3 in a fraternity of three.

Case 13, A.K., female. She had always had bad eyesight. She was deaf and dumb, otherwise healthy. She was well proportioned. Her mother had no disease during pregnancy.

37 *years old*: No nystagmus. Corneal-diameter normal o.u.

O. dext. There was a greyish opacity of about 3 mm. diameter in the anterior polar region of the lens. In the posterior cortex there was a rosette-like opacity. The nucleus of the lens was opaque. The fundus could not be seen.

O. sin. Corresponding picture.

It was difficult to obtain information about vision. The right eye was operated upon: Extractio cataractae. After operation retinitis pigmentosa was found. Vision: with + 14 she was able to read big print.

Diagnosis: Cat. congenita (pol. ant. et cort. post.). Retinitis pigmentosa. Surdo-mutitas.

Pedigree information. See Fig. 9.

The pedigree information covered six generations. The patient was No. 3 in a fraternity of three. Her eldest sister, K.P., 50 years old, her husband, H.P., 60 years

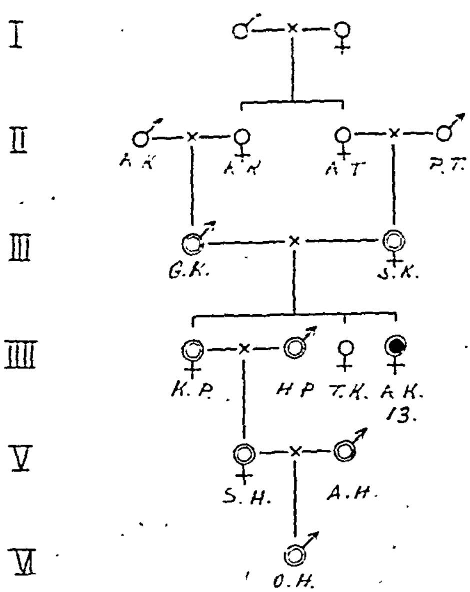

FIG. 9.

Family 9. Pedigree demonstrating that the parents of Case 13, A. K., female, with congenital cataract, were first cousins.

old, their daughter, S.H., 24 years old, and her husband, A.H. (28 years old) were all normal, together with their child, O.H., 4 years old. No. 2, T.K., female, died aged 31 years, but had good eyesight. The patient's parents, G.K., male, 70 years old, and S.K., 78 years old, had normal eyes. They were first cousins. The Patient's grandparents (gen. II) all died at advanced ages (64, 81, 84 and 83 years) and were said to have had good eyesight. Two of these, K.K. and A.T., were sisters. The descendants from these two were traced as far as possible and no other cases of cataract or other eye-disease were found.

In this family one sister among three had cat. congenita, (cat. pol. ant. et cort. post.). Retinitis pigmentosa and surdo-mutitas. The patient's parents were first cousins.

Family 10: *Case* 14.

S.B., female, born April 1, 1928, in Holla, Telemark. She was the only child.

Case 14, *S.B.*, female. During pregnancy the patient's mother had eclampsia. Spontaneous delivery. No infectious disease (*e.g.*, rubella). The mother noticed nystagmus in her child at birth. The child was admitted to a clinic 9 months old.

9 *months old*: Nystagmus. Total opacity of lens. Discissio cataractae o.u.
6 *months old*: Disc. cat. o.u.
9 *years old*: The patient was feeble minded. Not able to speak. Refused use of glasses. The pupillary-area was clear. Fundus appeared normal o.u. Nystagmus. Corneal diameter small ($8\frac{1}{2}$ mm.). Otherwise somatically normal.
Diagnosis: Cat. congen. (total). Imbecillitas.
Pedigree information. See Fig. 10.
The patient was the only child. Her parents, E.B., male, 45 years old, and K.B., 43 years old, were normal. The first one had four siblings, all normal. The second one had five siblings, all normal. There was no indication of relationship between the parents. The patient's paternal grandparents, R.B. and S.B., were both dead. The first one of pneumonia, 53 years old, and the second of apoplexia, 46 years old. Both of them had good eyesight. The patient's maternal grandparents were H.D., 80 years old, alive, with normal eyes, and M.D., who died 83 years old and had good eyesight. The paternal great-grandfather, H.D., 80 years old (gen. I) was still alive and had normal eyes. The other members of this generation died at

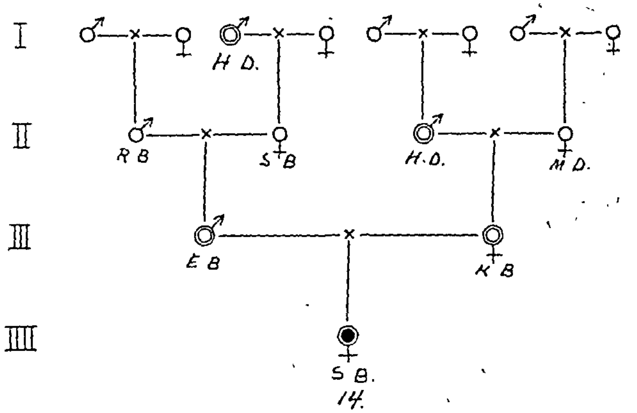

FIG. 10.

Family 10. Pedigree concerning Case 14, S. B., female, with congenital cataract. No consanguinity between the parents traced.

advanced ages and were supposed to have had good eyesight. The descendants from these were traced, but no other cases of eye-diseases were found.
In this family there was one case of cat. congenita (totalis) and Imbecillitas diagnosed. No indication of relationship between her parents.

Family 11: *Case* 15.
A.K., female, born May 2, 1924, in Gjerpen, Telemark, and was No. 2 of two siblings.
Case 15, *A.K.*, female. No indication of spasms or rickets in childhood. The patient's mother was healthy during pregnancy. For many years her eyesight was poor specially in bright day-light.
24 *years old*: Looked healthy. No nystagmus. Corneal diameter normal. There was a posterior cortical opacity in the lens. Otherwise the lens was clear. Fundus normal. The opacities were alike in both eyes. Vision: o.d = 5/10; o.s. = 5/10.
Diagnosis: Cat. juvenilis (cat. cort. post.).
Pedigree information. See Fig. 11.
Investigations through four generations were made. The patient's brother, K.K., 37 years old, his wife and their two children (aged 3 and 5 years) were all normal. Her parents, A.K., male, aged 67 years, and T.K., 70 years old, were both normal. Her father had two siblings, G.K., who died 74 years old, and K.K., 67 years old,

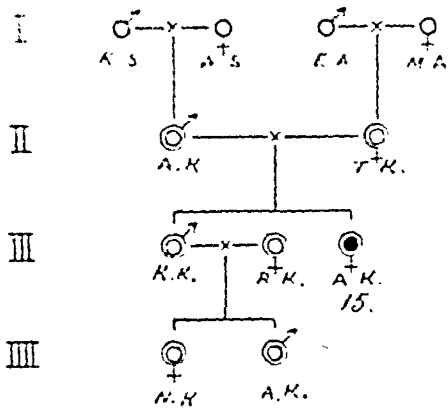

FIG. 11.

Family 11. Pedigree concerning Case 15, A. K., female, with congenital cataract. No consanguinity between the parents traced.

both of which had good eyesight. Her mother had five siblings. Two of these died at advanced ages, but had good eyesight. Three were still alive, passed 60 years of age, and had normal eyes. Information indicated that the patient's grandparents died at advanced ages, and had good eyesight. The descendants were traced as far as possible, but no other eye-diseases were found. No consanguinity between the patient's parents was discovered.

One case of cat. juvenilis (cat. cort. post.) was diagnosed. No indication of relationship between the patient's parents.

Family 12: *Cases* 16, 17, 18, 19 *and* 20.

A.T., female, born April 24, 1903, I.T., female, born January 1, 1905, A.T., born June 30, 1907, S.T., male, born April 28, 1914, in Seljord, Telemark. They were No. 2, 3, 4 and 8 in a fraternity of eleven.

Case 16, *A.T.*, female. The cataract was noticed at birth. Had otherwise been healthy. No spasms or rickets in childhood. Able to read a little. The patient's mother was healthy during pregnancy. She was admitted to a clinic when 6 years old and then operated upon.

45 years old: Well proportioned and healthy looking. Nystagmus present. Corneal-diameter normal o.u. Left eye in divergens.

O. dext.: There was a dense secondary cataract in which there were two holes about 3 mm. in diam. Fundus appeared normal.

O. sin.: The pupil was peripheral, as a small coloboma. Fundus could not be seen. Vision: o.d. + 14 = 5/30; o.s. + 14 C.F. at 4 m. With + 14 D lens she was able to read big print.

Case 17, *I.T.*, female. The cataract noticed at birth. Otherwise she had been healthy. No spasms or rickets. Her mother healthy during pregnancy. Operated on at 3 years old in the left eye and 7 years old in the right eye. Able to read and carry out housework.

43 years old: Nystagmus. Corneal diameter normal o.u. Well-proportioned and healthy-looking.

O. dext.: Anterior chamber deep. Pupil was round and dark. Fundus appeared normal.

O. sin.: Divergent strabismus. Anterior chamber deep. The pupil was peripheral as a small coloboma. There was a secondary cataract. Vision o.d. + 12 = 5/5; o.s. + 12 = 5/20.

Case 18, *A.T.*, female. The cataract noticed at birth. Otherwise of good health. No spasms or rickets. Her mother was healthy during pregnancy. The patient was operated on at 5 years old. Good vision post-operatively.

41 *years old*: Well-proportioned and looked healthy. Nystagmus present. Corneal-diameter normal o.u.

O. dext.: Ant. chamber deep. Round pupil with clear pupillary area. Fundus appeared normal.

O. sin.: Deep anterior chamber. Round pupil, with faint secondary cataract. Fundus looked normal.

Vision o.d. + 12 = 5/6; o.s. + 12 = 5/20.

Case 19, *S.T.*, male. The cataract noticed at birth. Otherwise healthy. No spasms or rickets. His mother healthy during pregnancy.

His eyes were operated on at the ages of 5 and 15 years. His eyesight remained poor, but he was able to read big print with a magnifying glass.

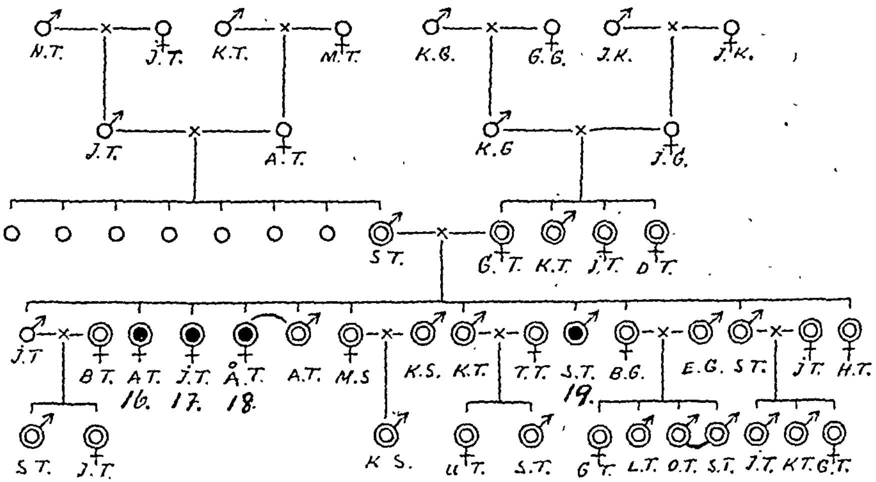

FIG. 12.

Family 12. Pedigree concerning Cases 16, A. T., female, 17, J. T., female, 18, A. T., female, 19, S. T., male, all with congenital cataracts. No consanguinity between the parents traced. S. T. (gen. III), aged 72, had senile cataract.

34 *years old*: He was well-proportioned and looked healthy. Nystagmus present. Corneal-diameter normal o.u.

O. dext.: Ant. chamber deep. Dense sec. cataract. Fundus was barely seen o.u.

Vision: o.d. + 12, count fingers at 3 m.; o.s. + 12 count fingers at 2 m. Discissio cataractae was advised.

Diagnosis: Cataractae congenitae.

Pedigree information. See Fig. 12.

The pedigree information covered five generations. The four patients had seven siblings, all normal. The patients were No. 2, 3, 4 and 8. No. 1 died 32 years old of tuberculosis. His wife and their two children (23 and 19 years old) were normal. No. 5, A.T. (twin of case 3) was normal. No. 6, M.S., 39 years old, and her husband and their children (4 years old) were normal. No. 7, K.T., his wife and their two children, aged 1 and 2 years respectively, were normal. No. 9, B.G., 33 years old, her husband, and their four children (twins), aged 6, 4 and 3 years, were normal. No. 10, S.T., 31 years old, his wife, and their three children aged 1 to 5 years, were normal. No. 11, H.T., 25 years old, was normal.

The patient's father, S.T., 72 years old, had cat. senil. incip. with wedge-shaped opacities in cortex.

Vision: o.d. = 5/6; o.s. = 5/10. Read easily. Seven of his siblings died between birth and 3 years (Diphtheria, scarlatina, cholera, etc.) The patient's mother,

G.T., 68 years old, had normal eyes as also her three siblings, aged 66, 64 and 62 years. These three had thirteen children, all normal. The patient's paternal grandparents had good eyesight. The grandfather died 47 years old of pneumonia. The grandmother 38 years old of tuberculosis. The paternal great-grandparents died at the ages of 59, 91, 85 and 64 years, and had good vision. The maternal grandparents also had good eyesight. The grandfather died 64 years old (K.G.), and the grandmother 79 years old. The individuals in gen. I died all at advanced ages, 74, 64, 68 and 80 years old, and had good eyesight.

Investigations indicated no relationship between the patient's parents.

In this family four of eleven siblings had cat. congenita. Their father had cat. senil. incip. No consanguinity between the patient's parents was indicated.

Family 13: Cases 20 and 21.

T.H., female, born 1938, and O.H., male, born 1941, in Hjartdal, Telemark, were No. 2 and 4 in a fraternity of four.

Case 20, T.H., female. The cataract was noticed before the age of one year. No spasms or rickets in childhood. The patient's mother was healthy during pregnancy. The patient's eyes were operated on at the ages of 4½ and 5½ years. Afterwards she had good eyesight.

9 years old: Well-proportioned and looked healthy. Corneal-diameter normal o.u. In both pupillary areas there was a fine membrane of sec. cataract. Discissio cat. o.u. was performed. Vision o.d. = 5/10; o.s. = 5/10.

No indication of the type of cataract was obtainable.

Diagnosis: Cat. congenita.

Case 21, O.H., male. The cataract was noticed before the age of 1 year. He had always been healthy. No spasms. No indication of rickets. His mother was healthy during pregnancy.

4 years old: He looked healthy. Well-proportioned. Nystagmus present. The corneal-diameter normal o.u.

O dext.: In cycloplegia a central, nuclear opacity was seen in the lens, measuring about 5 mm. in diameter. No riders. Red reflex in the periphery.

O. sin.: The same picture. Vision: C.F. at 2 m. o.u.

Diagnosis: Cat. congenita (nuclearis).

Pedigree information. See Fig. 13.

The pedigree information covered three generations. The patients had two normal siblings, No. 1 and 3, 12 and 6 years old respectively. Their father, O.H., 40 years old, and his six siblings were all normal. Their mother, A.H., 35 years

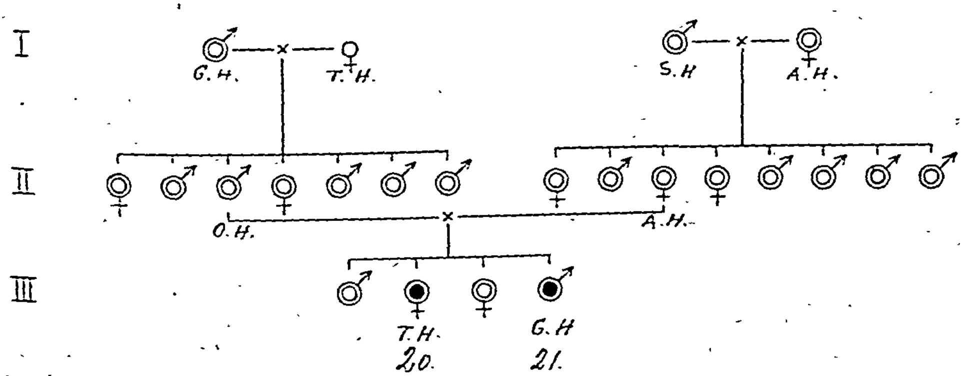

FIG. 13.

Family 13. Pedigree concerning Cases 20, T.H., female, and 21, G. H., male, both with congenital cataracts. No consanguinity between the parents traced. A sister of T. H.'s father (gen. I) had senile cataract. (Aged 65 years).

old, and her seven siblings were also normal. The paternal grandfather, G.H., 81 years old, was normal, and his wife, T.H., who died 60 years old, had good eyesight. A sister of the latter's father had cat. senilis, was operated on and regained good eyesight. The maternal grandparents, S.H., male, aged 64 years, and A.H., 64 years old, were still alive, and had normal eyes.

No indication of consanguinity between the patient's parents. The decendants from first generation were traced, but no evidence of cataract was noted.

In this family there are two cases of congenital cataract (nuclear) in a fraternity of four. No consanguinity between the patient's parents was indicated. One case of senile cataract far back in the family.

Family 14: *Case* 22.

A.S., female, born August 4, 1911, in Solum, Telemark. The patient was No. 7 in a fraternity of nine.

Case 22, *A.S.*, female. The patient's mother informed us that her daughter's eyesight was poor from childhood, and that she left school on that account at the age

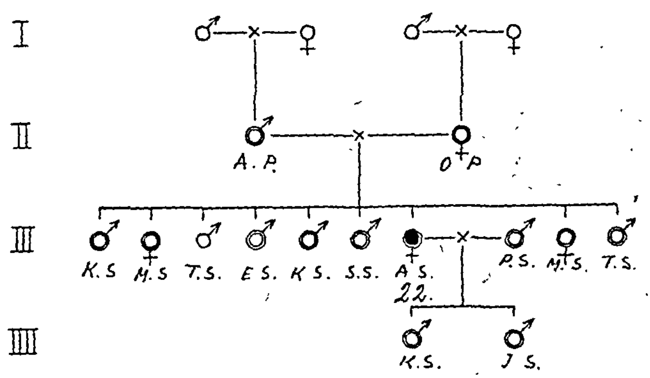

FIG. 14.

Family 14. Pedigree concerning Case 22, A.S., female, with juvenile cataract. No indication of relationship between her parents.

of 11 years. Spontaneously the mother also had asked the patient to state that she had spasms as a child and later also had rickets. The mother was healthy during pregnancy.

25 years old: She looked healthy and was well-proportioned. No nystagmus. Corneal diameter normal o.u.

O. dext.: In cycloplegia a typical perinuclear opacity of 5 mm. diameter, with riders, was seen. Red reflex around the opacity. *O. sin.*: same picture. Vision: Counting fingers at 3 m. o.u. Discissio et evacuatio cataractae o.u. was performed.

Vision: o.d. + 12 = 5/10; o.s. + 12 = 5/10.

Diagnosis: Cat. juvenilis (zonularis).

Pedigree information. See Fig. 14.

The pedigree information covered four generations. Her husband, P.S., was normal, as were their two children, aged 16 and 9 years. These had always been healthy, and were well-proportioned. The patient was No. 7 in a family of nine. No. 1 and 2 of these, aged 47 and 44 years respectively were normal. No. 3 died 8 days old. No. 4, 5 and 6 were 40, 38 and 36 years old, and were normal. So also were No. 8 and 9, 34 and 29 years old respectively. The patient's parents, A.P., male, aged 70 years, and O.P., 69 years old, were normal. The patient's grandparents died at advanced ages, and had good eyesight. There was no indication of relationship between the patient's parents. In addition to this information, the ascendants and descendants were followed as far as possible, and no other case of eye-disease was discovered.

In this family one patient with cat. juvenilis (zonularis) in a fraternity of nine was found. No consanguinity between her parents was indicated.

Family 15: Case 23.

I.K., male, born November 24, 1919, in Porsgrunn, Telemark, was No. 4 in a fraternity of five.

Case 23, I.K., male. The patient's mother informed us that he had spasms as a nursling and later rickets. Was healthy later in childhood. Attended the elementary school, but had poor vision. His mother was healthy during pregnancy.

25 years old: Well-proportioned. Looked healthy. His teeth, however, demonstrated severe enamel defects. No nystagmus. Corneal diameter normal o.u.

O. dext.: Cycloplegia. A central perinuclear opacity of 5 mm. diameter in the lens was seen. Within this a lot of powdered opacities. Typical riders around the opacity. Fundus was normal.

O. sin.: Corresponding opacities. Vision: o.d.=5/15; o.s.=5/10. Able to read.

Diagnosis: Cataractae juvenilis (zonularis).

Pedigree information. See Fig. 15.

This pedigree information was followed through three generations. The patient's four siblings: No. 1, I.K., female, aged 39 years, No. 2, A.K., male, aged 35 years, No. 3, N.K., female, aged 32 years, and No. 5, B.K., female, aged 22 years, were

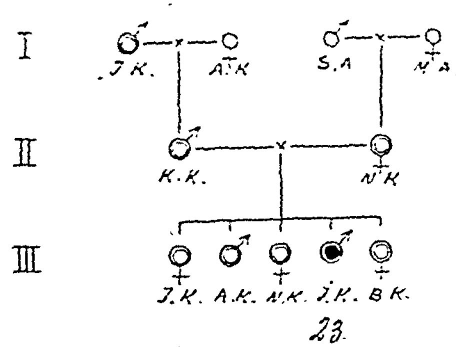

FIG. 15.

Family 15. Pedigree concerning Case 23, J. K., male, with juvenile cataract. No indication of relationship between his parents. J. K., gen. I, aged 91, had senile cataract.

all normal. They were all unmarried. The patient's parents (K.K., male, aged 64 years, and N.K., 64 years old) were normal. Of the patient's grandparents, only I.K., 91 years old, was still alive. He had cat. senil. incip. The other three died at advanced ages, 84, 82 and 87 years. They all had good eyesight. Their descendants were traced as far as possible and no other eye-diseases were discovered. No consanguinity between the patient's parents was found.

In this family there was one case of cat. juvenilis (zonularis), and one case of cat. senilis (in the paternal grandfather). No consanguinity between the patient's parents. The patient was said to have had spasms and rickets in childhood and demonstrated enamel defects of his teeth.

Family 16: Cases 24 and 25.

H.H., female, born April 11, 1927, and W.H., male, born 1925, in Brevik, Telemark, in a fraternity of two.

Case 24, H.H., female. The patient had always been of good health. No spasms. No rickets. She had good eyesight until 18 years old, when she noticed blurring before her eyes, and became tired on reading. Her mother was healthy during pregnancy.

20 years old: Looked healthy and was well-proportioned. No nystagmus. Corneal-diameter normal o.u.

O. dext.: In the central part of the lens, there was a perinuclear opacity corresponding to the foetal nucleus. (See Fig. 16a.) Around this was a layer of fine powder-like opacities. In the periphery there were more riders. These riders were supposed to be located around the infantile nucleus.

Fundus appear normal. *O. sin.*: Corresponding opacities in the lens. Vision =5/6 o.u.

Diagnosis: Cat. juvenilis (cat. zonular.).

Case 25, *W.H.*, male. He had always been healthy. No spasms or rickets. Had good vision until recently, when he became tired on reading and noticed blurred vision at distance.

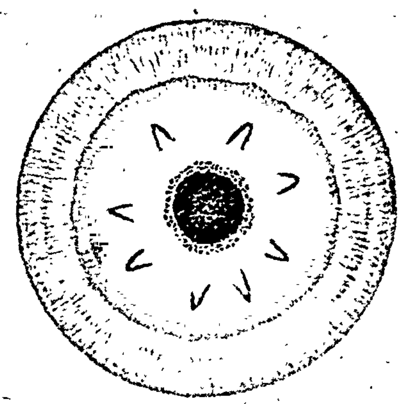

FIG. 16a.

Case 24, H. H., female, aged 20 years, with a particular type of zonular cataract. Her brother, Case 25, W. H., aged 16 years, demonstrates a similar cataract.

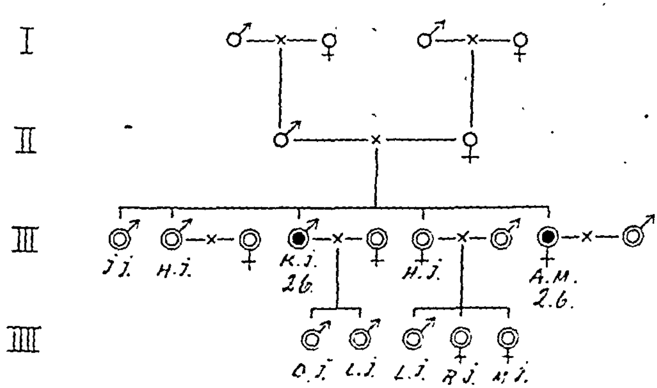

FIG. 16.

Family 16. Pedigree concerning Cases 24, H. H., female, and 25, W. H., male, with juvenile cataracts. No indications of relationship between their parents.

16 *years old*: He looked healthy. He was well-proportioned and had good teeth. No nystagmus. The corneal-diameter was normal o.u.

O. dext.: The clinical picture was here exactly the same as in his sister. There was a central perinuclear opacity with small powder-like opacities around this. Peripherally there were typical riders.

O. sin.: Similar opacities. Vision =5/6 o.u.

Diagnosis: Cat. juvenilis (zonularis).

Pedigree information. See Fig. 16.

The pedigree information covered three generations. The patient's parents, W.H., male, aged 52 years, and A.H., 46 years old, were both normal. There was no indication of relationship between these, as the first mentioned came from Sweden and the other from Norway. The patient's father had two elder brothers, who both died 62 and 57 years old respectively, one of tuberculosis and the other of heart disease. They had good eyesight. The patient's mother was No. 5 in a fraternity of seven. The other six were all examined. They were 60, 56, 53, 51, 38 and 36 years old and had normal eyes. Their children were also examined and demonstrated normal eyes. The patient's paternal grandparents died aged 67 and 84 years old. They had good eyesight. The maternal grandfather died 71 years old and had good vision. The maternal grandmother was still alive, 85 years old, and had normal eyes. The descendants from these were examined and no other cases of eye-diseases were found.

In this family both children in the family had exactly the same type of cataract, cat. juvenilis (zonularis). Consanguinity between the patient's parents was excluded. No indication of spasms or rickets in childhood.

Family 17: Cases 26 and 27.

K.J., male, born 1901, and A.M., female, born 1902, in Bamle, Telemark, were No. 3 and 5 in a fraternity of five.

Case 26, K.J., male. He had always been healthy. No spasms. No rickets. He had always had poor eyesight. Able to read moderately well at school. From the age of 25 years he was convinced that something was wrong with his eyes. His mother was healthy during pregnancy.

36 *years old*: Looked healthy and was well-proportioned. No nystagmus. Corneal diameter normal o.u.

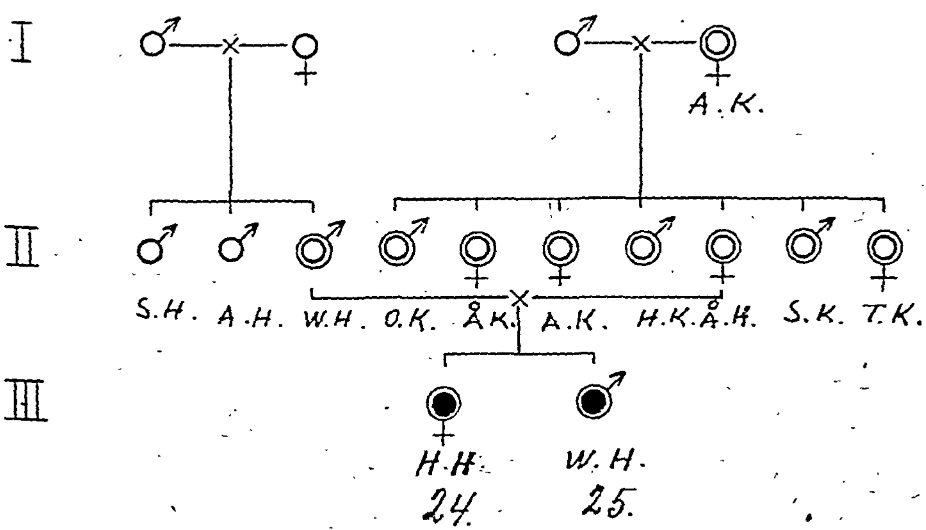

FIG. 17.

Family 17. Pedigree concerning the Cases 26, K. J., male, and 27, A. M., female, with juvenile cataracts. No indications of relationships between their parents.

O. dext.: Cycloplegia. A central perinuclear opacity of 5 mm. diameter. Some riders present. Red reflex around the opacity. Fundus appeared normal.

O. sin.: Corresponding opacity. Vision: o.d. + 3 = 5/20; o.s. + 3 = 5/15.

42 *years old*: The opacity more dense. Vision: + 3 = 5/50 o.u. Extractio cataractae performed on both eyes. Vision: o.d. = 5/15; o.s. = 5/10.

Diagnosis: Cat. juvenilis (zonularis).

Case 27, *A.M.*, female. She had always been healthy. No spasms. No rickets. Poor vision from the age of 17 years, specially in bright light. Her mother was healthy during pregnancy.

38 *years old*: Looked healthy and was well-proportioned. No nystagmus. Corneal diameter normal o.u.

O.U.: The lens opacities showed the same picture as in the above brother. Fundus normal. Vision: − 1 = 5/15 o.u. Extractio cataractae o.u. was performed. Vision: o.d. + 11 = 5/10; o.s. + 11 = 5/10.

Diagnosis: Cat. juvenil. (zonularis).

Pedigree information. See Fig. 17.

The pedigree data covered four generations. The patients were No. 3 and 5 in a fraternity of five. No. 1, J.J., male, aged 57 years, No. 2, H.J., male, aged 50 years, and his wife, 48 years old, had normal eyes. Case 26, K.F., had a wife 45 years old and two children, D.J., male, aged 25 years, and L.J., male, aged 14 years, all with normal eyes. No. 4, H.J., female, aged 42 years, her husband, 36 years old, and their three children, aged 13, 17 and 19 years, were all normal. No. 5 was the patient, Case 27, who was married, but had no children. The patient's parents died 80 and 77 years old and had good eyesight. Information about the patient's grandparents indicated no eye-disease. They died at advanced ages, and probably had good eyesight.

In this family two cases of cat. juvenilis (zonularis) were diagnosed in a fraternity of five. No indication of relationship between the patient's parents. No indication of spasms or rickets during the patient's childhood.

DISCUSSION AND CONCLUSION

A. Heredity

In the introduction to this paper the confusion about the mode of heredity of congenital and juvenile cataracts was emphasized, the dominant mode being considered the most common. The recessive mode, however, was not considered to be worth investigating.

The present material is numerically too small to prove recessivity statistically. There were, however, many indications of its existence: pronounced familial incidence, frequent relationship between the parents of the affected individuals, and the fact that the cataracts in most of the cases were congenital.

In this material the familial incidences were prominent. In 8 of 17 examined sibships, 2 or more individuals were affected. This cannot be accepted as proof of inheritance — exogenous factors must also be taken into consideration — but it is very suggestive.

Among the exogenous (environmental) factors giving rise to congenital cataracts, special attention during recent years has been paid to the virus diseases (rubella). A considerable literature already exists on this subject, and a rather complete

list is presented by Bardram and Brändstrup (1947). There is, of course, no doubt that rubella in the mother during pregnancy may cause a congenital cataract, but in the cases presented this etiological factor can be excluded.

From the available literature in this field, it appears that the whole clinical picture caused by rubella is different from the clinical picture of the above cases. The cataracts caused by rubella usually are accompanied by considerable somatic defects and malformations, and hence must be considered a more serious disease. It is also evident from the present material that rubella cannot be made responsible for many congenital cataracts within the same sibship.

In the Table I below, the frequency of relationship between the parents of the affected individuals is demonstrated. In 5 of the 17 families the parents were first cousins. In another 4 they were related further back. Consanguinity was found, therefore, in 9 of the 17 families. Taking into consideration the remarks made in the introduction about the rare occurence of consanguinity, these facts are of great interest, and may indicate recessive heredity.

TABLE I

Number of children, number of cataracts, application of Weinberg's methods, and intermarriages in 17 families with congenital and juvenile cataracts.

Fam. No.	No. of Children (S)	No. of Catar. (T)	Weinberg's Meth.		Intermarriages in Parents
			T (S—1)	T (T—1)	
1	3	2	4	2	First cousins
2	2	1	1	0	Third cousins
3	4	2	6	2	First cousins
4	2	1	1	0	Fifth cousins
5	1	1	0	0	Fourth cousins
6	3	2	4	2	Second cousins
7	9	2	16	2	First cousins
8	5	1	4	0	First cousins
9	3	1	2	0	First cousins
10	1	1	0	0	No
11	2	1	1	0	No
12	11	4	40	12	No
13	4	2	6	2	No
14	8	1	7	0	No
15	5	1	4	0	No
16	2	2	2	2	No
17	5	2	8	2	No
Total:	70	27	106	26	

nucleus, which develops between the 3rd and 8th months of foetal life. Peripherally in the lens some riders were seen. These riders are supposed to be located in the area of the infantile nucleus, which develops between the last weeks of foetal life and puberty. These findings may give the impression that some agents have been active at different periods. It does not disprove, however, that these cataracts may be due to genes.

In the present cases of zonular cataracts dominant mode of heredity is not indicated. Recessivity may be present, but cannot be proven. Neither can the effect of spasmophilia or rickets be assessed. Even if the aetiology of zonular cataracts is more obscure than that of other congenital or juvenile cataracts recorded in this paper, they are—with reservation—listed together in a common group.

As the patients were treated surgically in different clinics, and descriptions of the various types were often lacking, the differential diagnosis was rather difficult to make. With these reservations in mind, it would seem that the cataracts were of the same type within the same family. Thus, the type was considered to be similar (cat. subtotalis) in patients Nos. 1 and 2 in family No. 1. The cataracts were congenital and the two patients were both operated on at the same age (3 years). In the families Nos. 2 and 3, which were related, the cataracts also were congenital, and the patients were operated on at the same ages (2, 3 and 2 years). The diagnoses made were: cat. subtotalis, cat. membranacea and cat. totalis. In family No. 6 the diagnoses in Cases Nos. 8 and 9 were cat. nuclearis. Both were congenital and were operated on at the age of 9 and 5 years, respectively. In family No. 7 (Cases No. 10 and 11) the diagnoses were cat. corticalis and polaris ant., and the cataracts were of the same type. In family No. 12 (Cases Nos. 16, 17, 18 and 19) no diagnosis was made as to the special type, but they were all considered to be the same, as they were all congenital, and were operated on at the same ages (6, 3, 5 and 5 years, respectively).

In family No. 13 (Cases Nos. 20 and 21) the diagnosis was cat. nuclearis. Both of them had congenital cataracts. One of the patients was operated on when 4 years old, the other was ready for operation at a corresponding age. In family No. 16 (Cases Nos. 24 and 25) the zonular cataract was precisely of the same type in both brother and sister. In family No. 17 (Cases Nos. 26 and 27) there was a zonular cataract of the same type in both sister and brother. These cataracts were diagnosed and operated on at the same age. The type was, however, quite different from the one in the previous cases. Accordingly, the present

cases show that the types of cataracts vary from family to family, but within the same family the congenital or juvenile cataracts are much alike. These observations support the above-mentioned hypothesis that these cataracts are probably due to genes, and that there is no genetical connection established between these and the sporadic senile cataracts occurring in these families.

B. Occurrence of other diseases or symptoms in cataract patients

The occurrence of spasmophilia, rickets and enamel defects of the teeth has already been mentioned.

In one of the patients (Case No. 14) glaucoma was diagnosed. In two of them (Cases Nos. 12 and 13) the cat. corticalis posterior et polaris anterior was combined with retinitis pigmentosa. Case No. 13 also demonstrated surdo-mutitas.

As to the connection between the cataract and retinitis pigmentosa, two possibilities exist:

1. The cataract is correlated to retinitis pigmentosa.
2. The cataract is secondary to retinitis pigmentosa.

It is generally accepted that retinitis pigmentosa is as a rule a recessive condition. Kjerrumgard (1948) has found that 9 per cent. of all patients with retinitis pigmentosa demonstrated cat. pol. post., and that 5 per cent. of them had other types of cataract. He also demonstrated that 15 per cent. of the patients with retinitis pigmentosa had surdo-mutitas.

In our two cases of retinitis pigmentosa and cat. pol. post. there was also a cat. pol. ant., a type usually considered to be congenital. It is therefore reasonable to suggest that cat. pol. post., cat. pol. ant., retinitis pigmentosa and surdo-mutitas are correlated and that they are due to recessive genes.

Nystagmus was noted in 12 of the 27 patients and occurred only when combined with congenital cataracts.

Microphthalmos was found in 2 patients (Cases Nos. 6 and 14). Minor variations in the corneal diameters may have been more frequent, but exact measurements were not undertaken.

C. The prognosis

The results of the cataract operations were good, except in the following patients: Case No. 21, who was not operated upon; Case No. 14, who was feeble-minded; Case No. 9, with glaucoma; Case No. 19, with cataracta secundaria; Cases Nos. 12 and 13, with retinitis pigmentosa. Most of the operated patients were able to read and do full-time work in their different occupations.

In these conditions, therefore, the only advice to be given from

the eugenic point of view is to warn members of the families against inter-marriages. But as already noted, dominant types of congenital cataracts are likely to exist, and the mode of heredity in each case must be thoroughly investigated.

D. Conclusion

In the introduction it is shown how uncertain is the etiology and pathogenesis of congenital and juvenile cataracts. The dominant mode of inheritance is preponderant, and the recessive type of cataract is relatively rare.

Even if the material dealt with in this paper is too small to give proof by statistics, a series of cases of congenital and juvenile cataracts is cited which seems to indicate recessive inheritance.

Summary

The author of this paper has examined 17 families in which congenital or juvenile cataract occurred. Special attention was paid to their aetiology and mode of heredity.

In the introduction a review of the previous results from literature in this field was given. This showed that the dominant mode of inheritance is supposed to be the most frequent, with relatively rare examples of recessive inheritance. In recent years much attention has been paid to the virus diseases as causes of these cataracts, and inheritance has receded more into the background.

Exogenous factors, as spasmophilia and rickets, were suggested causes of zonular cataracts, but the rôle of heredity was also emphasized in this type.

Following this introduction, a review is given of the present material and the case reports with pedigrees.

In all, 17 families with 27 cases of congenital or juvenile cataracts have been examined. From these, 20 were recorded as congenital and 7 as juvenile. In each of 8 of these families, 2 or more individuals were affected. Among the 27 affected, 14 were males and 13 females.

In 9 of the 17 families, relationship between the parents of the affected individuals existed, and in 5 of them the parents were first cousins. In the other 4 families the relationship was less close.

In a following chapter, "Discussion and Conclusion," the results of these investigations were stated. Among the introductory remarks it was pointed out that the present material is too small to prove statistically the probable mode of inheritance in the cases investigated in this survey. As a eugenic measure,

the members of these families must be warned against intermarriage, but, as dominant types also occur, it is emphasized that the mode of inheritance must be studied in each case.

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THE MOTOR IMPULSE ELICITED BY THE RETINAL STIMULUS AND THE BINOCULAR OPTICAL REFLEXES*

BY

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IN order to study the problem of strabismus, it is necessary to investigate the disturbances of the normal binocular reflexes which occur in such patients. To do this, however, an exact knowledge of the essential features of these binocular reflexes in normal persons is required.

We started from the fundamental supposition that stimulation of a certain part of the retina not only produces a sensory effect, but is also active in a motor sense. In our opinion stimulation of the retina gives rise to a sensory *and* a motor impulse. There is evidence that in general these motor impulses may produce the following four physiologic phenomena:

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Objectively:

I. A sidewards movement of equal amplitude and in the same direction of both eyes; a conjugate movement.

II. A movement of the eyes in opposite direction: disjunctive movement; this results in a fusional movement.

Subjectively (when the motor effect on the muscles is inhibited).

III. Localisation of the stimulus in space.

IV. The visual sensation of apparent movement.

We have investigated three of the four reactions (II, III and IV). In the course of our experiments it appeared that in haploscopic alternating stimulation of both retinas with a small luminous spot we had an excellent method for analyzing these reactions.

Description of the Apparatus.

A narrow strip of wood was fixed on a wooden frame, forming part of the circumference of a circle. Two wooden boxes may be shifted along this strip. Each box is provided with a small hole of 3 mm. diameter in the centre. These holes are covered by transparent paper and are illuminated by a $3\frac{1}{2}$ volt lamp within the boxes. An alternating device was incorporated in the electrical circuit; this makes it possible to illuminate the boxes alternately. The alternating device is driven by a motor (M) with adjustable speed; by lowering or increasing the speed of the motor the frequency of alternation can be controlled. The latter is measured by a revolution-counter (R), which may be placed on the axis of the alternating device (A). The experiments were carried out in complete darkness. The image of the luminous spot intended for the one eye was screened from the other eye by the interposition of screens (S). Fig. 1 shows the test set-up. By proper adustment of the screens we can stimulate "binasally" (each eye sees homonymous objects) or "bitemporally" (each eye sees heteronymous objects). Both methods of stimulation are shown in Fig. 2. The interval between stimuli was made equal to zero as near as possibile. When, under these circumstances, we apply alternate haploscopic stimulation to the eyes with a low frequency of alternation (*e.g.*, each retina receives 20 stimuli in 30 seconds), maximal apparent movement results. When the frequency of stimulation was raised we noticed the following phenomena:

The amplitude of the apparent movement was reduced, whereas the movement retained its optimal character; the subject still had the impression of one object moving over a certain distance. The distance across which the movement was seen, however, lessened.

A further increase of the frequency reduced the amplitude still more, until one object exhibiting slight movements was seen. Still further increase of frequency caused the movement to disappear completely and only one motionless object was seen. These effects resulted from a fusional movement; the motor impulses roused by the alternating retinal stimulation found a concrete expression in this fusional movement.

Increase of frequency, however, may also be followed by another phenomenon. Instead of apparent movement over a smaller distance, simultaneous perception of two objects at the original distance may result (*sim-stadium* of Wertheimer). This simultaneous perception of two objects is still accompanied by some apparent movement. The two objects appear to "jump" towards their place and away from it. ("Aufauch" and "Erlösch-Bewegung," Roelofs and Van der Waals.)

A further increase of frequency then results in simultaneous perception of two objects separated in space, without any apparent movement.

Summarizing:

Low frequency—maximal apparent movement of one object.

Increase of frequency—either apparent movement over a smaller distance or simultaneous perception of two objects accompanied by "jump" apparent movement.

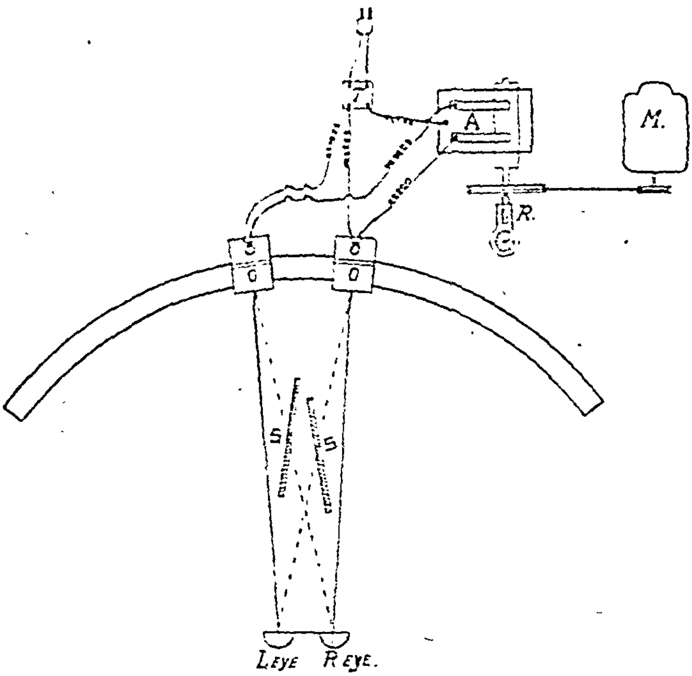

Fig. 1.

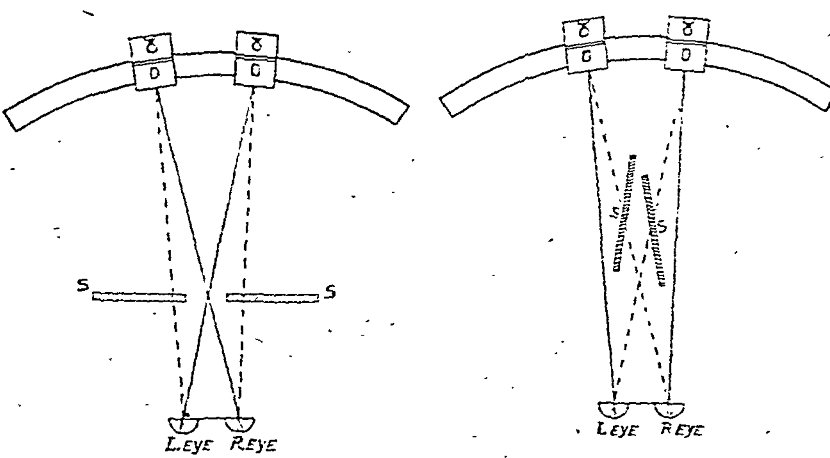

Fig. 2.

Further increase—either one motionless object or two motionless objects separated in space.

It depends on the outer circumstances which of the two reactions is chosen. The frequency of alternating stimulation is of great significance with regard to the reaction. The maximal apparent movement seen with low frequency is gradually transferred to the standstill of one object with increase of frequency. In our experiments we tried to establish the frequency of the alternating stimuli required for the different phases of the above mentioned process.

The following steps were paid attention to:

Increase of frequency	1. Maximal apparent movement (m)
	2. Initial shortening of amplitude of the apparent movement—first symptom of a fusional movement—(m + f)
	3. Complete standstill of the object—fusion is complete—(f)
Lowering of frequency	4. Reappearance of apparent movement after the standstill—described by the subject as "slight movement"—(f + m)
	5. Maximal apparent movement (m)

The experiments were carried out with "bitemporal" as well as "binasal" stimulation (see Fig. 2). The distance between the subject and stimulating objects was 2,89 M. The distance between the objects corresponded to a visual angle of 1° 5′ (55 mm.) and also 2° 22′ 40″ (12 cm.). The frequency of stimulation is expressed in the number of stimuli per 30 sec. falling on each retina. The experiments were also carried out with a red and a green object.

In Table I the results of the experiments are given. Each line in the table contains the mean values of a series of experiments carried out in one session.[3] The apparatus was only used in preliminary investigations. In further experiments the objects were projected on to a screen by means of a projection-tachystoscope. In this method the wooden boxes with a 3 mm. diameter hole were substituted by luminous spots of 3 mm. diameter projected on to a screen. In all other respects the test set-up was the same as in the preliminary experiments. All figures of Table I were obtained by experiments with the projection-tachystoscope. Our subject had a slight exophoria (Maddox right eye: 36′; left eye: 24′).

	m + f	f	f + m	m
BITEMPORAL STIMULATION				
Visual angle 1°5′	85	114	103	27
	74	118	111	65
	75	117	100	58
	92	124	100	56
	96	126	108	64
Visual angle 2°22′40″	44	112	—	—
Coloured objects (red and green)	80	112	—	—
BINASAL STIMULATION				
Visual angle 1°5′	51	117	91	31
	58	120	99	26
	42	122	111	18
	32	112	—	—
	44	120	110	28
Visual angle 2°22′40″	21	112	—	—
	30	110	106	20

TABLE I

From this table we may conclude:

1. Alternate stimulation with a frequency of 10-20 stimuli per 30 sec. on each retina brings about maximal apparent movement.

2. A shortening of the amplitude of this apparent movement occurred on bitemporal stimulation with 74-96 stimuli per 30 sec. on each retina with objects subtending 1° 5′; for a visual angle of 2° 22′ 40″ a shortening occurred with 44 stimuli. On binasal stimulation these values were 32-58 stimuli/30 sec. for a visual angle of 1° 5′ and 21-30 st./30 sec. for a visual angle of 2° 22′ 40″.

These values mark the beginning of fusional movements.

3. One motionless object was seen when the frequency was 112-126 for bitemporal stimulation; and 110-122 for binasal stimulation.

These values marked complete fusion of the objects.

4. Lowering of the frequency made the movement appear again. Initial movement occurred with 91-111 stimuli on binasal stimulation and 100-108 stimuli on bitemporal stimulation. With this frequency the motor impulses were no longer strong enough to maintain complete fusion.

5. A further lowering of the frequency results in apparent movement with maximum amplitude. This occurred on bitemporal stimulation with a frequency between 17-65, and on binasal stimulation between 18-31.

6. With coloured objects (one eye was stimulated by a red, the other by a green object), a blending of colours occurred with the same frequency, which caused a fusion of the white objects. This suggested that motor and sensory fusion here occurred with the same frequency.

Fusional movement, however, did not always occur according to this scheme. Fusional movement was impaired especially when the darkness in the room was not complete. In these circumstances increase of frequency resulted in simultaneous perception of both objects, accompanied or not by "jump" apparent movement (see also page 630). In this case the motor impulses elicited by haploscopic alternate stimuli of both retinae followed a different reflex-path. The motor impulses did not bring about a fusional movement (reaction II, see page 630), but led to a localisation of both objects separated in space (reaction III, see page 630). The same phenomenon could be observed if one retina only were stimulated alternately by two objects. With low frequency, maximal apparent movement was seen, with increase in speed of alternation, "jump" apparent movement together with simultaneous perception of both objects separated in space resulted. A further increase gave simultaneous perception of two objects without any apparent movement. In case of stimulation of one retina, reaction III only is elicited.

We then investigated whether the same frequency, which brings about a fusional movement, may also by following another reflex-path give rise to the simultaneous perception of two objects separated in space. For this purpose we drew a comparison between haploscopic alternate stimulation of both retinae and alternate stimulation of one retina only. In case of the former the motor impulses follow the reflex-path of reaction II; with the latter it was reaction III.

We therefore investigated the effect of monocular alternating stimulation in the same way as in the binocular experiments. The right and left eyes were investigated separately and the investigations were performed with and without a fixation-point. The fixation-point made it possible to investigate the effect on the temporal and nasal half of the retinas and also the effect of one stimulus falling on the nasal half and the other on the temporal half of the retina. The objects subtended a visual angle of 1° 5′. The test set-up was the same as in the binocular experiments, the only difference being that one eye was covered and the screens were removed. The results given in Table II are quoted under five headings:

	m	m+s	s	s+m	m
WITHOUT FIXATION POINT					
R. eye	20	32	108	92	48
L. eye	24	44	92	80	40
WITH FIXATION—POINT					
nasal half of retina:					
R. eye	—	24	104	76	28
L. eye	20	48	100	96	16
temporal half of retina:					
R. eye	28	44	96	92	40
L. eye	—	20	120	96	16
temp. + nas. halves of retina:					
R. eye	20	36	88	72	32
L. eye	20	40	84	60	32

TABLE II

maximal apparent movement (m); increase of frequency: apparent movement + simultaneous vision (m + s); simultaneous vision without movement (s); lowering of frequency: simultaneous vision + apparent movement (s + m); maximal apparent movement (m).

These results were compared with the values of the binocular experiments quoted in Table I:

Monocular altern. stim.		Binoc. haplosc. binasal stim.		altern. stim. bitemp. stim.
m + s :	20-48	m + f .	32-51	74-96
s :	84-120	f :	110-122	112-126
s + m :	60-96	f + m :	91-111	103-111
m :	16 48	m :	18-31	27-65

Considering that it is very difficult for the subject to indicate when he sees two objects without apparent movement (s) and two objects with slight apparent movement (s + m), we may conclude that the values in the two columns fairly agree. These values indicate that the beginning of a fusional movement (m + f) and the beginning of simultaneous perception (m + s) occurred with about the same frequency of alternation. We may substitute fusion (reaction II) for simultaneous perception (reaction III). In both instances the stimuli are the same; they give rise to identical motor impulses which, however, may follow two reflex-paths—one leading to reaction II (fusion) and the other to reaction III (simultaneous perception). In case of monocular alternate stimuli only reaction III is available, but in binocular haploscopic stimulation reaction II or reaction III may be chosen. It depends on the outer additional circumstances which reflex-pathway is used. When the room was not completely darkened, reaction III (simultaneous perception of two objects) was favoured. In a following article we will prove that this was caused by additional peripheral stimuli from the surroundings. If the influence of these peripheral stimuli was excluded by using a completely darkened room, reaction II (fusion) always occurred.

These experiments concerned fusion and movement in the horizontal direction. We repeated the same experiments with the stimuli placed vertically, one above the other. The experiments for the vertical direction yielded results which were similar to those in the horizontal direction. To obtain fusion in the vertical direction, however, it is necessary to use a smaller distance between the stimulating objects.

Conclusion and Summary

A theory on the binocular optical reflexes is presented. Each retinal stimulus gives rise to a sensory *and* a motor impulse. This motor impulse may be responsible for the following reactions:

(I) A sidewards movement of both eyes in the same direction.

(II) A movement of both eyes in opposite directions. These movements may, however, be inhibited, in which case the motor impulse gives rise to

(III) Localisation of the stimuli separated in space,

(IV) The perception of apparent movement.

An investigation of reactions II, III and IV was carried out by means of alternate haploscopic stimulation of both retinae. By varying the speed of alternation of the stimuli, it was possible

to analyze the conditions for fusional movements. Haploscopic stimulation with low frequency of alternate stimuli gives rise to reaction IV (maximal apparent movement). Increase of frequency results in a combination of reaction IV with *reaction II (apparent* movement combined with a fusional movement) or in a combination of reaction IV with reaction III (apparent movement together with simultaneous perception). A further increase of frequency causes reaction IV to disappear and fusion (reaction II) or simultaneous perception of two objects (reaction III) results. Reactions II and III occur with the same frequency of alternate stimuli and are brought about by motor impulses of the same quality and quantity. These motor impulses may follow different reflex-paths leading to reaction II or reaction III. Additional circumstances may inhibit one reflex-path and favour the other; *i.e.*, alternate haploscopic stimulation of both retinae in a completely darkened room results in reaction II; if the room is not completely darkened reaction III is favoured.

According to this theory and based on experimental evidence, fusion, localisation and apparent movement are explained as physiological rather than psychological phenomena. They are optical reflexes, of which the physiological correlate is provided by the motor impulses elicited by the retinal stimuli.

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HYALINE MEMBRANES ON THE POSTERIOR CORNEAL SURFACE

BY

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LONDON

HYALINE membranes attached to the posterior corneal surface and spanning the anterior chamber are striking curiosities. They may arise (1) as persistence of embryonic tissues, (2) as detachments of Descemet's membrane and endothelium, or (3) as sheets of inflammatory exudate; the following three cases illustrate each of these groups, and the aetiology is discussed.

CONGENITAL HYALINE MEMBRANE

Case History. A man, aged 31 years, whose right eye had been divergent and almost blind since infancy, showed the following abnormal signs in that eye.

Behind the axial area of the cornea lay a semilunar transparent membrane, joining the cornea along a line that passed from 11 to 7 o'clock, roughly concentric with the limbus, 1-3 mm. internally, and merging there with the posterior corneal band. The free margin ran vertically to connect either end of the attached margin: in the centre of this free margin, overlying the pupil, was a small area of pigmented tissue, resembling persistent pupillary membrane, and from it a brown cord passed deeply and downwards to reach the lesser circle of the iris at 6 o'clock. There were no keratic precipitates, and the corneal diameter was 12 mm., as compared with 13·5 mm. in the other eye. The pattern of the iris was less well marked than in the other eye, and there were three clumps of axial epicapsular stars on the lens. The eye was highly myopic (−9·0 D.), and even this correction did not improve his vision beyond finger-counting. There was a divergent concomitant strabismus of 20°, rectified by operation, and a coarse latent nystagmus.

His father and grandmother also had divergent squints, but the father's eyes were otherwise normal.

Abscission of the membrane was performed on July 7, 1948; the attached edge was divided by the sweep of a Ziegler's needle-knife, and a few days later the whole membrane was lifted out through a keratome section, the cord to the iris being divided with scissors. It now became possible to see the fundus, which showed extensive myopic choroido-retinal degeneration, and no visual improvement ensued. (See Figs. 1 and 2.)

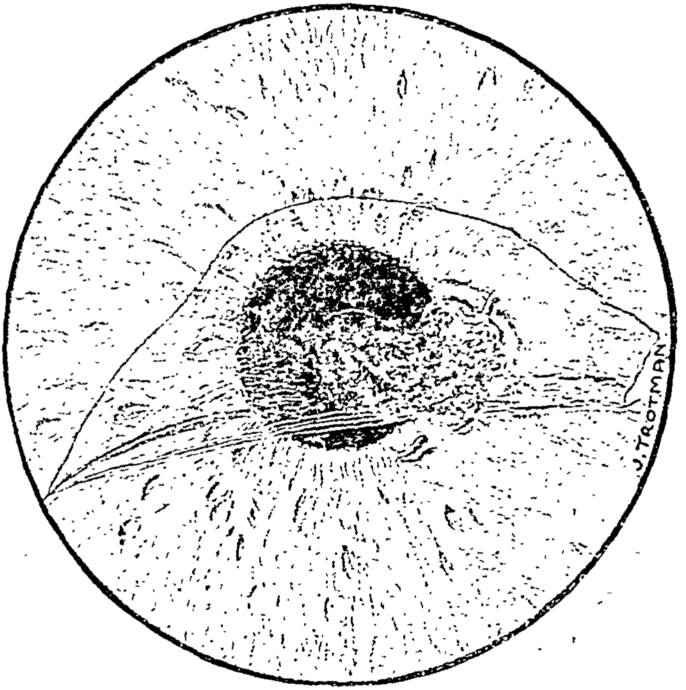

FIG. 1.

FIG. 2.

DISCUSSION. During development the lens vesicle becomes separated from its parent surface epithelium, and the intervening space is traversed by the protoplasmic threads of the mesostroma or the anterior vitreous body, which is ectodermal in origin. This mesostroma is most evident peripherally, filling the space where the curve of the lens bends away from the surface ectoderm. A directional membrane is formed by a condensation of the mesostroma, whose anterior surface remains in continuity with the epithelium, but whose posterior surface becomes separated from the lens by a space created by atrophy of the cones of the lens epithelium, from which it partly originated. The mesodermal masses lie peripherally, and grow in centripetally both along the posterior surface of the directional membrane as the future endothelium of the cornea; and later, anteriorly to the endothelium, appearing as a wedge of nuclei separating endothelium from epithelium, and ultimately compressing the mesostroma, which it invades, into the condensations of Bowman's and Descemet's membranes. Finally the mesoderm of the iris and pupillary membrane grow in from the post-endothelial mesodermal condensations.

Persistence of the post-endothelial tissues may occur, and thus present as a fluffy mesh occluding the angle and liable to produce glaucoma; the congenital hyaline membranes described in the literature—Mann (3 cases), Ballantyne, Clapp, Hagedoorn—are all of this order, and in all of them the hyaline membranes were present beneath the cornea at its periphery only, and never extended more than a few mm. from the limbus. Only Ballantyne's case (six days old, with lid and iris colobomata), had keratic precipitates. The other patients were more mature, three showing characteristic thickened ridges on the iris, and one a band which passed forwards to the cornea. The post-endothelial tissue is abundant only peripherally, where these anomalies developed, but the foregoing case, where only central anomalies are present and the characteristic iris anomalies are absent, is not easy to explain in this way.

The mesostroma over the centre of the lens is very thin, as the lens remains almost in contact there with the parent ectoderm, separated from it only by the endothelium, and consequently an incomplete separation of the membranous pupillary membrane from the endothelium is likely to occur, with the result that an anterior synechia of pupillary membrane to endothelium, and subsequently of the mesodermal pupillary membrane and secondarily of the iris will result. This would seem to explain the origin of the case I have reported; for it may be surmised that subsequent development of the eye, with deepening of the anterior

chamber, caused the endothelium and Descemet's membrane to be thereby stripped off the cornea by traction of the synechia over the area where the anterior chamber was deepest.

The cornea of the affected eye was significantly smaller than its fellow, in spite of the high myopia, and a similar feature was noted in one of Miss Mann's patients. If it had been unduly large, one might have guessed that the membrane was stripped off like a retinal detachment in an elongating myopic eye, but the small cornea is presumably evidence only of underdevelopment of the anterior segment, as often happens with persistent embryonic tissues. Such congenital membranes might result from an intra-uterine inflammation, with the anterior iris synechia as evidence of this, and the membrane as a secondary detachment through traction; but apart from the synechia (which in both the foregoing case and the case of Miss Mann's in which it was described was large, single, and free from inflammatory irregularities) and the keratic precipitates in the infant described by Ballantyne (which does not fall so readily into this group), there were no signs of inflammation. The membrane reported bore little resemblance to the true inflammatory sheets of interstitial keratitis, etc., as will be evident when this group is discussed.

Divergence of the eye in the above case is probably not due to impaired binocular vision caused by the membrane, but coincidentally to an hereditary monocular myopia, since his father and grandmother had divergent eyes but no membrane.

DETACHMENTS OF DESCEMET'S MEMBRANE

Hyaline membranes can be present since birth, not as a congenital defect, but resulting from birth trauma after distortion of the eye with forceps: into this category falls the following case, where a very similar membrane was found behind the centre of the cornea in an eye which had also been divergent and weak-sighted since infancy.

Case History. A man, aged 20 years, with a divergent and partially blind left eye, ascribed his disability to a forceps delivery.

A semilunar transparent membrane lay behind the central area of the cornea, joining it along a line that passed from 10.30 to 5.30 o'clock from the corneo-scleral margin at either end, but 3 mm. internal to it laterally; there it merged with the posterior corneal band. The free margin connected the ends of the attached margin, and was curled over on itself, so that it appeared double in the slit-lamp beam. Another line curved nasally from the upper limit of the membrane to just short of the lower limit, and appeared to be a thickening of Descemet, skirting peripherally a similar semilunar area. A dust-like opacity was present in the middle of the corneal thickness over the whole pupillary area; there were no keratic precipitates. A pulverulent opacity was present in the anterior foetal nucleus of the lens. The iris and fundus were normal. The eye

was highly astigmatic ($-1\cdot5$ D.S., $+5\cdot0$ D.C. at 110°), but this correction did not improve his vision beyond finger-counting.

A 40° divergent concomitant squint was rectified by operation. The right eye was normal and emmetropic, and there was no relevant family history. (See Figs. 3, 4 and 5.)

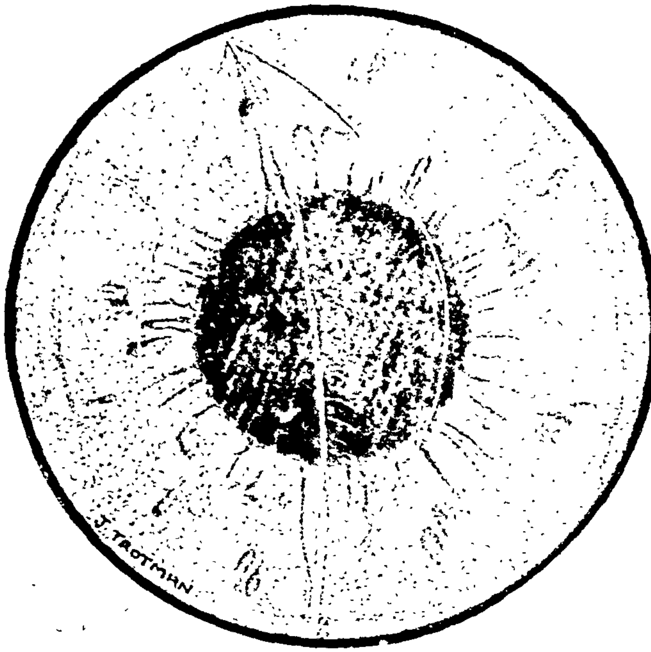

FIG. 3.

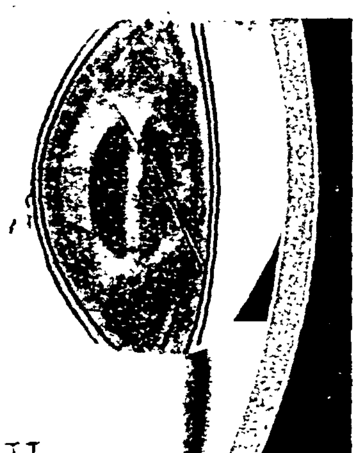

FIG. 4.

FIG. 5.

DISCUSSION. Thomson and Buchanan described three varieties of birth injury to the cornea, in all cases following difficult labour and the use of forceps: (1) A diffuse opacity which is temporary, and due to oedema. (2) A similar diffuse opacity which becomes permanent through superadded inflammation. (3) An opacity which is linear and permanent, and due to rupture of Descemet with or without the posterior corneal lamellae. Subsequently cases were recorded in which tears of Descemet were followed by its detachment over a wide area. This usually produced a series of vertical ribbons between the parallel tears, which were attached only at their upper and lower extremities (Peters, Feingold, Lloyd, Rushton, Perera, Fison): these bands tended to roll up into rods if they were narrow, so that a colonnade seemed to grace the forecourt of the eye. In other cases, as in that described here, a falciform or segmental detachment was present, again with the long axis roughly vertical. (Ballantyne, Fewell.)

All such birth injuries of the cornea are becoming less common as rickety pelves become rarer, and accoucheurs become more deft and less reliant on forceps. These lesions occur predominantly in the left eye, as in the above case and in Lloyd's five cases, since the left occipito-anterior position is commonest, bringing the left eye laterally. The damage is probably caused by pressure directly on the cornea by the long axis of the forceps blade—so everting and vertically splitting the inner layers.

In the above case the nasal edge of the torn Descemet's membrane has remained (as usual) as a small ridge through the greater part of the extent of the original tear, while temporally the membrane has become detached over a wide area. The fine powdery opacity in the *substantia propria* of the area that has been denuded is typical of those cases of more severe damage, where some fibrosis has followed the initial oedema. There is also the characteristic high astigmatic error (5·0 D.C.) in the slightly oblique axis of the tear, such uni-ocular astigmatism being sometimes attributed *per se* to obstetric pressure; and there is characteristically no mesodermal abnormality.

INFLAMMATORY RETROCORNEAL MEMBRANE

Case History. A man, aged 59 years, with a classical history of interstitial keratitis—bilateral "blindness" at the age of 13 years, which after two years cleared gradually in the left eye only, and an acknowledged parental infection with syphilis—showed the following appearance.

The right eye was blind, and directed 15° upwards and 15° convergent. Both corneae were slightly ectatic, with characteristic interstitial nebulae, some deep attenuated blood-vessels, and, in each eye, an eccentric deposit of blood pigment. Over the back of the right cornea stretched a reticulate sheet, the interlacing fibrinous bands being as wide as the holes that separated them. They adhered to the posterior corneal surface except at a very few points, where a gap between

band and Descemet's membrane was discernible; these bands became fainter peripherally, where the cornea was relatively clear.

Over the back of the left cornea were fewer but more discrete interlacing strands, spanning the anterior chamber like a cobweb so that centrally they lay well behind the cornea. Inserted, as they were, into the latter at either end, they seemed to consist of a fine opaque white central filament with a relatively broad translucent sheath.

Both irides were atrophic, especially on the right side, with posterior synechiae also on that side. Exudate on the anterior lens capsule, cortical cataract and a small bound-down pupil prevented a view of the right fundus, and this eye had no perception of light. The left lens was clear except for a few epicapsular stars. The left fundus was normal centrally, but showed extensive peripheral disturbance from old anterior choroiditis. The left vision was improved to 6/18 with $-5{\cdot}5$ D.S. correction.

In spite of having had no specific treatment, he was otherwise healthy, except for deafness on one side. His Wassermann reaction was negative. His mother and father had "died of drink" when he was young, but his brother, aged 66 years, was alive and well, and also showed on examination a typical interstitial keratitis, although much less intense, the vision being 6/60 and 6/24 with myopic correction. There were no comparable abnormalities in the brother's eyes, except for a fine translucent strand passing in the right eye across the pupil from one posterior synechia to another, and jutting forward into the anterior chamber, so that it was well clear of the lens capsule. (See Figs. 6, 7, 8, 9.)

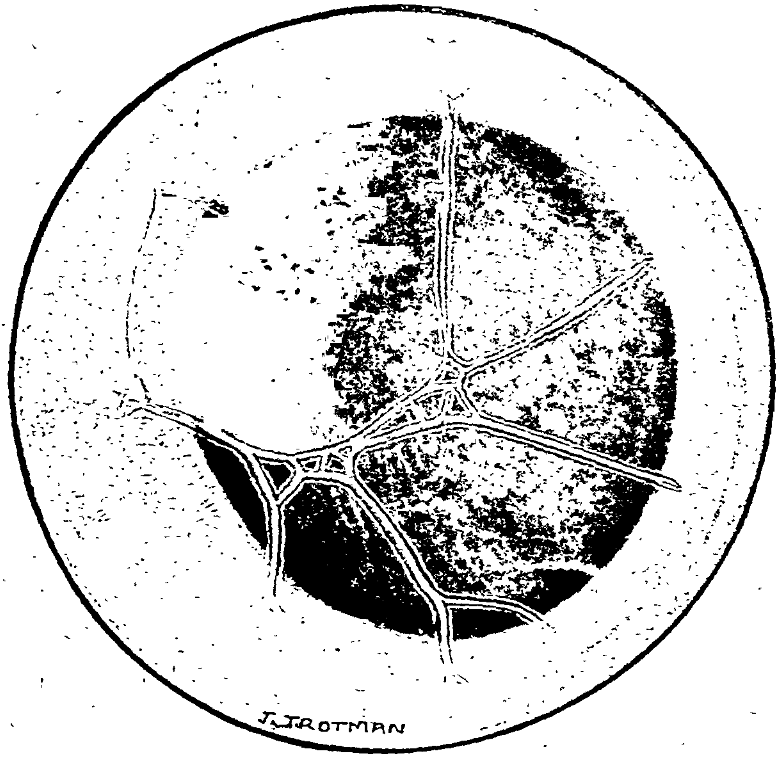

FIG. 6.

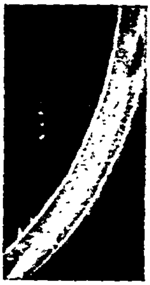

FIG. 7.

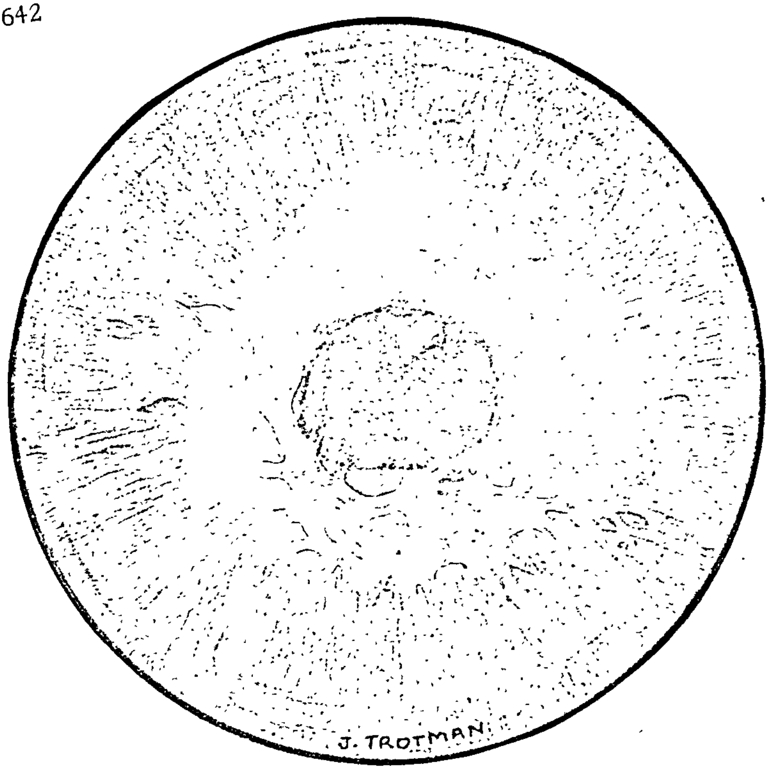

Fig 8.

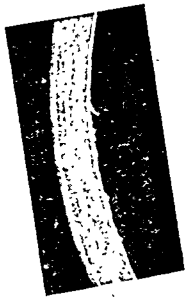

FIG. 9.

DISCUSSION. Membranes from inflammatory exudate are considerably less rare than the two varieties already described, and are more frequently recognised in the literature, so that little comment is here required. Typically they are seen as irregular fibrinous laminae, reticulate or stellate, and not as an even and thin semilunar sheet. Commonly they admit the term "glass membrane."

They occur classically in interstitial keratitis, but are occasionally described in tuberculous or other forms of intense uveokeratitis. They lie behind the centre of the cornea, and are necessarily associated with other signs of past inflammation. Initially they were probably wholly in contact with the endothelium, but become detached like the strings of a bow when their fibrin content subsequently retracts. It is of passing interest to note the fibrinous filament in the anterior chamber of the brother's eye, but here passing between two posterior synechiae instead of between two points on the posterior corneal surface.

Perhaps the precipitation of fibrinous shreds depended on an hereditary predisposition or on the particular strain of spirochaete.

My acknowledgments are due to I. C. Mann for necessary advice and assistance, and to E. F. King and A. G. Cross for permission to use their case-records.

Summary

Three cases are described of hyaline membranes; one of them a consequence of developmental arrest, one due to birth trauma and the third following uveokeratitis. Their aetiology is discussed.

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LOCAL APPLICATION OF UREA FOR THE TREATMENT OF DENDRITIC ULCER*

BY

M. KLEIN *and* S. J. H. MILLER

LONDON

HYPERTONIC solutions applied in an eye-bath are believed to have a favourable influence on marginal ulcers of the cornea. One obvious advantage of an eye-bath is that the medication is kept in the conjunctival sac. A series of cases of dendritic ulcer was treated with a corneal bath containing a 25 per cent. solution of urea in 1942-44 at the Central London Ophthalmic Hospital and the results in over 30 cases were encouraging.† The same treatment has been carried out in a new series, and the results are reported here. It

* Received for publication, April 11, 1949.

† M. Klein. Results unpublished, as the notes of these cases were lost during the war.

appears that urea, though widely used in other branches of medicine, has not been employed in ophthalmology.

Historical.—The effect of urea on bacteria has been known for many years. Ramsden (1902) noted that urea inhibited putrefaction. According to Peju and Rajat (1906) urea added to a nutritive medium produces abnormal morphological forms, and if the concentration is increased the growth of bacteria stops altogether. Wilson (1906) noted that 1·5 to 3·5 per cent. of urea in the medium caused pleomorphism, and an addition of 8 per cent. urea prevented the growth of B. coli. In 1915 Syms and Kirk observed that 25 per cent. or stronger solutions of urea killed B. typhosus, and local applications of crystalline urea resulted in the sterilization of wounds. Foulger and Foshay (1935) treated purulent otitis media by local application of saturated solutions of urea, and McKay and Schröder (1936) found that concentrated urea solutions inactivated rabies and poliomyelitis virus in a relatively short time. The use of urea gained popularity recently when it was found that it increased the activity of locally applied sulphonamides, and a dusting powder consisting of urea and sulphonamide was widely used for wound treatment during the late war. Weinstein and his co-workers (1944-1947) studied the antibiotic activity of urea and its related compounds (urethane and thiourea) and found that the antibiotic effect of these preparations is considerable and is mainly directed against Gram-negative bacteria. Gram-positive bacteria are affected only by exposure to higher concentrations and for longer periods (Weinstein and co-workers). Some of the urea derivatives, especially phenylurethane, can be regarded as poisons acting directly on the cell. Spores soaked in 0·5 per cent. urethane show effects similar to irradiation with 1,000 r X-rays (Haddow 1948). Urethane has also been administered in leucaemia and the effect is said to be comparable to that of deep X-ray therapy. (Paterson *et al.*, 1946.)

Properties of urea and its derivatives are as follows: Urea forms white hygroscopic crystals. Solutions must be kept sterile as they are liable to undergo ammoniacal decomposition if contaminated. Urea is a normal constituent of tissues and blood. It is not toxic, and if it is applied to wounds, healing is not interfered with. Thiersch grafts do not necrose in the presence of urea. Urea solutions are neutral and their antibiotic activity is retained in acid or alkaline media. Urea penetrates cells readily, *e.g.*, red blood cells, and the urea content becomes similar within and without. It does not cause haemolysis. The break-down products of tissues are dissolved in a solution of urea, a point of importance in the local use of sulphonamides. Clinically urea

solutions have proved useful in chronic purulent wounds: they stimulate healing and help in the separation of sloughs (Williams, 1946 and Robinson, 1936). Urea can be used with advantage in combination with sulphonamides, as it enhances their solubility and contributes its own bactericidal effect. It can also be used in combination with penicillin, and, according to Weinstein, urea limits the production of penicillinase. Derivatives of urea which have been used or investigated for antibiotic effects are : allantoin, urethane and phenylthiourea. The action of urea on wounds is the rationale of the present study.

LOCAL USE OF UREA IN CASES OF DENDRITIC ULCER

As in the preliminary series, the following method of treatment was used in the present series. The eye was anaesthetised with two instillations of 0·5 per cent. amethocaine hydrochloride B.P.

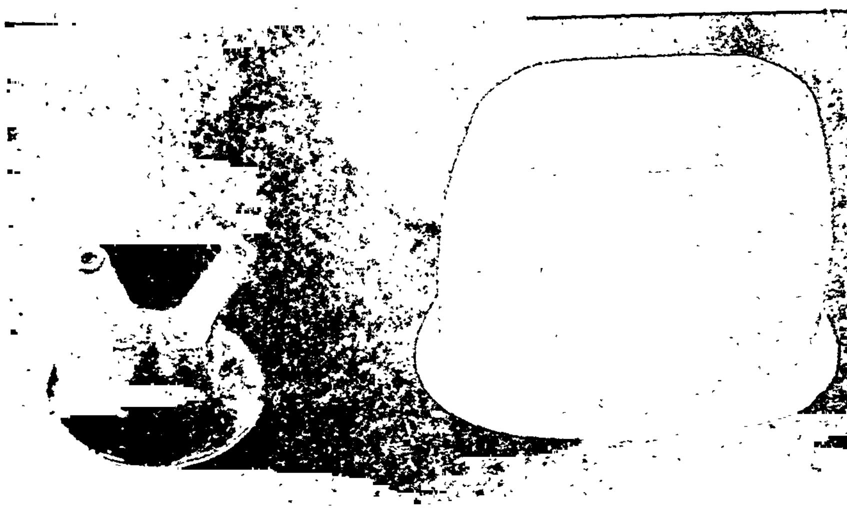

FIG. 1.

(*a*) Contact shell applicator. (*b*) Eyebath.

The contact lens applicator* was placed over the eye (Fig. 1a and Fig. 2) and filled with a freshly made solution of 25 per cent. urea to which 2 drops of amethocaine was added to each 5 ml. solution. The application was well tolerated and treatment was done either in the sitting or recumbent position. Through the transparent plastic contact applicator the eye was watched during treatment, and if the ulcer was not covered by the fluid the appli-

* Made by G. Nissel & Co., Ltd.

cator was replenished. The duration of the treatment was 5 minutes. Immediately after treatment the cornea usually showed diffuse staining round the dendritic ulcer, and very often a large adjacent area became denuded of epithelium.

In some cases there was difficulty in the use of the contact applicator, and a bakelite eyecup, the bottom of which was removed, was used instead (Fig. 1b and Fig. 3). After placing the cup over the open eyelids, the urea solution was poured into the cup. By

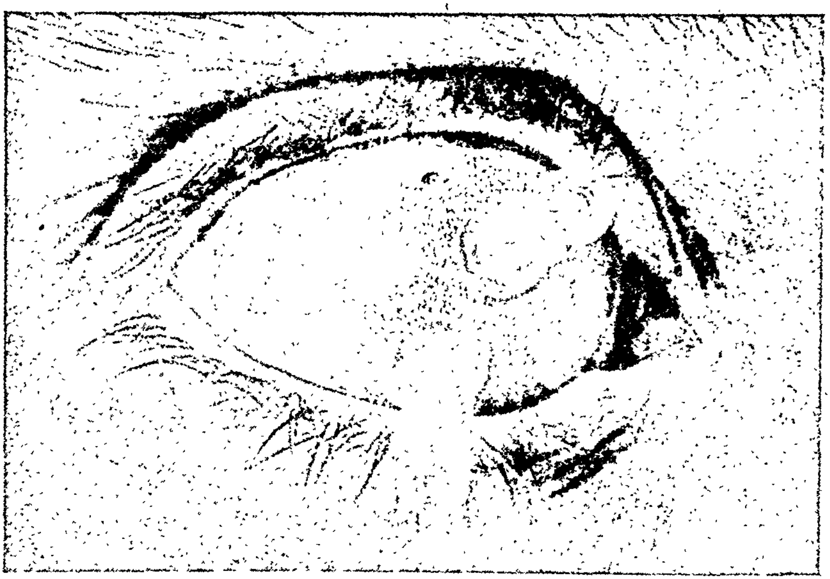

FIG. 2.

Contact shell applicator inserted without fluid. Condensation shows up the raised corneal portion.

a slight pressure with the edge of the cup the palpebral fissure was kept open so that the cornea was bathed with the fluid. With this treatment the patient had to be in a recumbent position.

The urea treatment was followed by instillation of 1 per cent. atropine drops, yellow soft paraffin was placed in the lower fornix and the eye bandaged. The dressing was changed after 24 hours, when the staining area was found to have diminished or completely healed over. A second or third urea treatment could be given with an interval of 24 hours between each treatment. A mild ointment such as yellow soft paraffin was useful in preventing the breaking-down of the newly formed epithelium.

FIG. 3.

Eyebath in use. The edges of the cup hold the palpebral fissure open.

RESULTS

Thirty-three cases were treated in this series arbitrarily divided into three groups according to the severity of the lesion. Group I included all the cases in which there was a well localized dendritic

TABLE I

Data on individual cases

No.	Age	Sex		Severity			No. of urea applications	Healing time in days	
		M.	F.	I	II	III			
1	45	M.	—	—	II	—	1	13	—
2	70	M.	—	—	—	III	—	40	See Remarks
3	30	M.	—	—	II	—	2	14	—
4	28	M.	—	—	—	III	2	28	See Remarks
5	35	—	F.	—	II	—	2	42	Healed 12 days after urea, See Remarks
6	71	M.	—	I	—	—	1	2	—
7	58	M.	—	I	—	—	1	2	—
8	46	M.	—	I	—	—	1	4	—
9	67	M.	—	I	—	—	1	3	See Remarks. Urea treatment was given 4 weeks after onset and 3 weeks after other treatment had failed.
10	62	M.	—	I	—	—	1	10	History of previous dendritic ulcers 1933, 1943, 1946.
11	63	M.	—	I	—	—	1	5	—
12	60	M.	—	—	II	—	1	28	History of previous dendr. ulc. See Remarks.
13	25	M.	—	—	II	—	1	7	Came to Hospital 1 month after onset.
14	62	M.	—	—	II	—	1	9	History of previous dendritic ulcer.
15	19	—	F.	I	—	—	1	7	—
16	38	M.	—	I	—	—	1	7	—
17	48	—	F.	—	II	—	1	28	Transient punctate staining of cornea. Hist. of prev. dendritic ulcer.
18	45	—	F.	I	—	—	2	16	Transient punctate staining of cornea.
19	61	M.	—	I	—	—	1	15	Transient punctate staining of cornea History of prev. corneal ulcers, ? nature.
20	24	M.	—	I	—	—	2	5	—
21	51	M.	—	I	—	—	1	7	—
22	51	M.	—	I	—	—	1	7	—
23	39	M		I	—	—	1	10	—
24	64	M.	—	I	—	—	1	11	—
25	70	M	—	I	—	—	1	5	—
26	68	M.	—	—	—	III	1	42	See Remarks
27	69	M.	—	—	II	—	1	13	Transient punctate staining.
28	52	—	F.	I	—	—	1	—	No response to urea, transferred to Radiotherapy
29	38	—	F.	I	—	—	1	7	—
30	38	—	F.	I	—	—	1	9	—
31	44	M.	—	I	—	—	1	17	—
32	53	M.	—	I	—	—	1	13	—
33	56	M	—	I	—	—	1	6	—

figure, Group II those in whom the lesion was more extensive, and Group III those with deeper lesions marked either by infiltrations of the deeper layers of the cornea, or by cells in the anterior chamber, or by hyperaemia and swelling of the iris without patent herpetic iritis.

REMARKS

(2) Recurrent dendritic ulcer; attacks almost every year since 1933. No response to treatment. Iodised six times, carbolised twice, urea applied three times, vaccinated, sulphacetamide locally applied, retrobulbar alcohol injected. Eventually the eye became quiet after tarsorrhaphy. Duration 40 days. Urea ineffective.

(4) First urea treatment on the fourth day after onset. The eye made a slow recovery and on the 21st day the ulcer recurred, for which a second treatment with urea was given. Two days later there was no staining. Received two urea treatments; healed in 28 days.

(5) October 17, 1947. Carbolised and local penicillin applied: October 20, 1947, vaccinated. One month after treatment had failed urea was applied, and 10 days later repeated. Rapid healing followed in a few days. A fortnight later a small staining area was noted, urea treatment was given again and healing followed.

(9) *Iodised twice, local albucid applied, without success. Three weeks after* treatment had failed, urea was applied and 3 days later there was no staining. Four weeks after discharge there was a relapse which healed without treatment in one week.

(12) After the first urea treatment the condition improved but the epithelium was constantly breaking down. Patient was treated with albucid, healing was slow, taking 4 weeks. History of dendritic ulcers previously.

(26) Had one urea treatment. After some improvement, the ulcer broke down and did not heal until intravenous ascorbic acid (500 mg. daily for 7 days) was given.

Group I was the largest with 22 cases. The number of days needed for healing varied between 2 and 16 after the application of urea, with an average of 8 days. In 20 cases one application of urea proved sufficient. The average healing period of 8 days applies to cases in which 6 or 8 days after the urea treatment, punctate staining appeared. In these cases the time was recorded when the corneal condition was completely healed.

Group II contained 8 cases. Healing time was protracted in two cases owing to a recurrence of the staining area. In the remaining cases of this group the healing time was from 7 to 14 days with an average of 15·5 days for the group as a whole.

TABLE II

Classified data on the patients in group

	Healing time in days			Distribution of age			Total	Distribution of sex	
	average	min.	max.	under 35	36-55	56 & over		Male	Female
Group I	8	4	16	2	11	9	22	18	4
Group II	15.5	7	42	3	2	3	8	6	2
Group III	36	28	42	1	—	2	3	3	—
				6	13	14	33	27	6

Three cases fell into Group III. The healing period was in one case 28 days, in the other two 6 weeks.

Discussion

In this series, dendritic ulcer was predominantly a disease of males, and mostly of the older age group, as can be seen from Table II. In those cases giving a history of one or more attacks of dendritic ulcer in the past the tendency to healing was poor. On the other hand, where the dendritic ulcer developed upon corneal scars of other than dendritic origin, the healing time was the same as on a previously healthy cornea. After urea treatment the epithelium quickly regenerated, and the ulcer healed, but there was a tendency to relapse, a well-known characteristic of dendritic ulcer. It was therefore deemed important to give protection to the corneal epithelium by placing in the lower fornix a mild lubricating ointment and to keep the eye bandaged for 6 to 10 days after complete epithelialization. Patients were then advised to continue the pad and bandage at nights only, for another 3 weeks.

An important factor in the healing of dendritic ulcers is the general condition of the patient; the most severe cases appeared to be in poor physical condition, and the corneal lesion healed only after general treatment was given. In two severe cases, 500 mg. ascorbic acid was given intravenously daily for 7 days, and rapid healing was observed. It appears that the essential points in the treatment are (1) the favourable effect of locally applied urea followed by (2) protection of the healed area by a lubricant and a bandage, and in severe cases by (3) general treatment in order to improve the physical condition of the patient.

The punctate staining which was seen in a few cases following urea treatment may have been caused by the use of urea from a stock solution; it is advisable to use solutions freshly made. Recently in the treatment room, packets of 1 gm. urea powder have been kept ready, and the solution made by adding 4 ml. distilled water immediately before use.

Summary

The use of 25 per cent. urea solution applied as a corneal bath by means of a contact applicator or an eyecup is suggested as a method of treating dendritic ulcer. This application lasts from 5 to 10 minutes. The urea solution should be freshly made. The urea treatment is combined with treatment by atropine, yellow soft paraffin and bandaging of the eye.

No damage was observed from the application of urea. Results of 33 cases are reviewed. The milder cases generally healed after one application.

Our thanks are due to the Surgeons of Moorfields, Westminster and Central Eye Hospital, High Holborn, for permission to treat their cases. We are indebted to Mr. W. E. S. Bain and Mr. D. Langley for their help in the treatment and for observation of some of these cases, and to Sisters E. Kitchen and P. Hollis. For the photographs we are indebted to Mr. Peter Hansell.

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THE RELATIVE IMPORTANCE OF DIRECT AND INDIRECT OPHTHALMOSCOPIC EXAMINATION IN THE TREATMENT OF RETINAL DETACHMENT*

BY

H. ARRUGA

BARCELONA

IT is essential to employ both methods of ophthalmoscopy to obtain the highest possible percentage of successes in the surgical treatment of retinal detachment. I have seen on my travels that many colleagues employ one method to the exclusion of the other, and that in some countries the majority of the ophthalmologists use one method almost exclusively. If we grant the enormous importance of ophthalmoscopic examination in the treatment of retinal detachment, we must also make as complete an examination as possible by this method. I have seen colleagues who, though excellent clinicians and surgeons, only reached 55 per cent. of successes in these operations, owing, in my opinion, to the exclusive use of direct ophthalmoscopy as a mode of operative orientation.

These facts decided me to prepare the statistics of 200 unselected cases of my own, which I had classified in the following four groups:—

The *first* group includes those cases in which tears were visible to either method of examination. In the *second* group tears were visible only to indirect ophthalmoscopy, and in the *third* only visible

* Received for publication, May 27, 1949.

to direct ophthalmoscopy. The *fourth* group includes cases in which tears were invisible to both methods.

The figures are as follows:—

Cases with tears which were visible by both methods	154
Cases with tears which were visible only by indirect ophthalmoscopy	25
Cases with tears which were visible only by direct ophthalmoscopy	3
Cases with tears which were invisible to both methods	18
Total	200

Of the 18 cases forming the fourth group, 11 were extremely old ones, with opaque vitreous or other opacities, and 4 of them were clearly cases of exudative choroiditis.

The advantage of indirect ophthalmoscopy can be deduced from these statistics. Direct ophthalmoscopy is an excellent method for appreciating doubtful details, such as haemorrhage, and in order to measure differences of retinal level. Indirect ophthalmoscopy, however, with its larger field, better view of the periphery, and the possibility of employing a high light intensity of 150-200 candle power, is the method which should be preferred, although one should not use it exclusively. Pictures are reproduced of six cases in which it was possible to make a drawing of the retinal tear. In the remaining cases the tear was too obscure to be truly represented in any drawing without falsifying the reality, and these latter cases formed the majority.

Examples of Cases With Tears Difficult to Diagnose

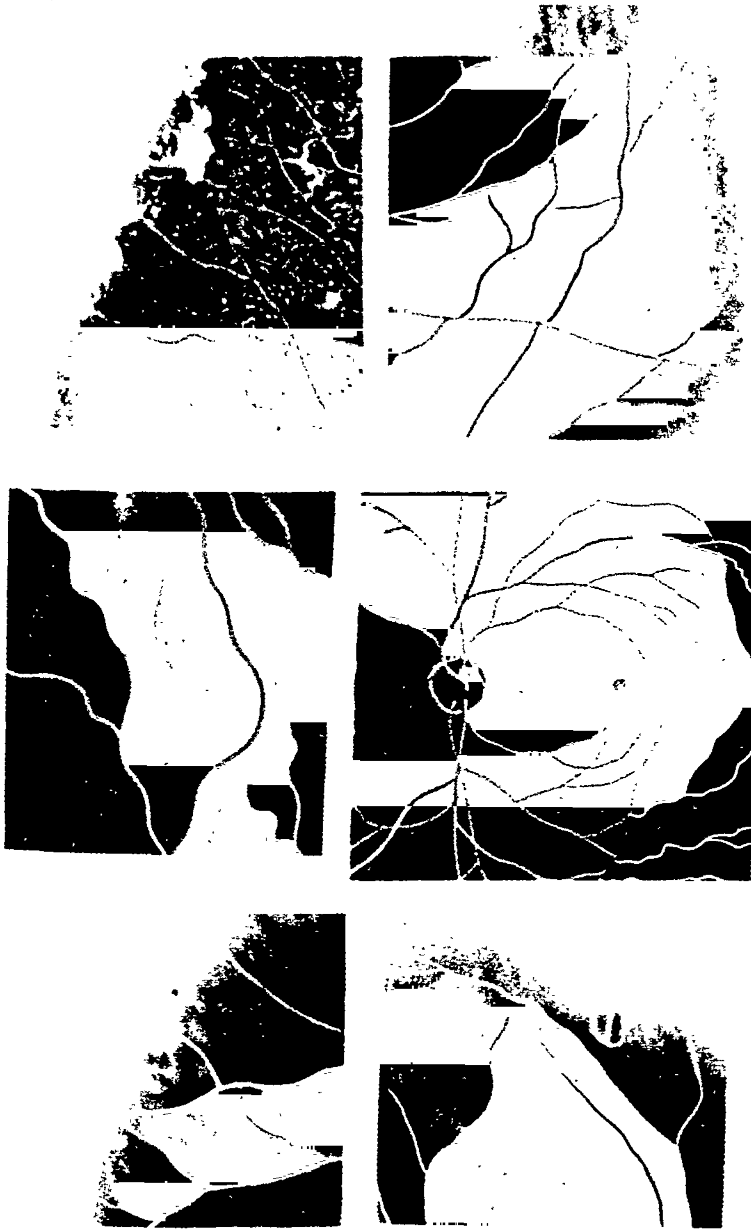
1. Tear near the ora serrata only visible with the indirect method. This represents a recurrence in an operated case. It was cured by diathermy.

2. Between the folds of the retina appeared a red line like a vessel. This sometimes disappeared, and it was only possible by the direct method to verify that it was a tear. During the operation the tear was half opened.

3. In the centre of the figure in a fold of the retina a tear with pigmented borders was recognised through the difference in level of its borders, no red coloration being seen. During the operation the tear was easily visible.

4. Detachment with large lateral disinsertion. The macula appeared perforated, but with direct ophthalmoscopy it was revealed as a cystoid degeneration without difference of level.

5. Tear only visible by indirect ophthalmoscopy, difficult to verify because there was a shallow detachment of the adjacent retina. The operative closure of the tear confirmed this diagnosis.



1 2

3 4

5 6

6. Tear near the ora serrata invisible with direct ophthalmoscopy. Except for the folds of the retina, it appeared like a spot of chorio-retinitis. Closure of the hole cured the detachment.

Professor Dr. JOSEF MELLER (Vienna)

It is pleasant to salute outstanding men, and readers will have noticed that several recent articles in the Journal were dedicated to the subject of this address. On behalf of his British colleagues, we thank Professor Meller for the example he has set, and in offering him congratulations on his seventy-fifth birthday (October 22, 1949) we wish him pleasant days in retirement. His work and character will be remembered for many years. On the occasion of the seventieth birthday of Ernst Fuchs, Meller wrote about his predecessor : " His name shines forth in our science as that of his great teacher von Arlt." Meller in his turn has carried on the outstanding work of the Vienna School.

Since 1898 until his retirement in October, 1944, he worked at the Eye Clinic of Vienna, except for a three-year period (1915 to 1918), when he was " ordinary " professor of ophthalmology at the Imperial and Royal University of Innsbruck, to which he had been appointed by the Emperor Francis Joseph. In 1918 he was appointed " ordinary " professor of Ophthalmology at the Imperial and Royal University in Vienna, but by a letter from the German Reichminister for Science and Education, Berlin, dated May 10, 1944, he was relieved of the post of leader and teacher in the Vienna Eye Clinic " in the interest of later development at the high schools," and he retired from his position on October 1, 1944.

Unfortunately he seldom visited this country, although he had a good command of English, but he attended the 50th Annual Congress of the Ophthalmological Society of the United Kingdom at London in 1930 and became known to many of the participants who recollect his qualities of sincerity, modesty and geniality. He was also seen at the Oxford Congress a few times, and contributed to important discussions at the meetings of that body. Many will remember his delivery of the 1934 Doyne Memorial Lecture, which emphasised the continental view that iridocyclitis is often tuberculous in nature (as is now agreed in this country). He also reported that in some such cases tubercle bacilli may be recovered from the blood and from the eye, and argued that sympathetic ophthalmia is also probably tuberculous—dicta not accepted without considerable reserve.

Meller succeeded Ernst Fuchs at Vienna, and maintained the outstanding reputation for clinical work, research and teaching which that centre had deservedly earned. The professor and his assistants spoke English, and held post-graduate classes which were especially appreciated by students from the United States.

His fame brought honours to him, and he was an honorary member of the Academy of Science in Vienna. He was an

honorary member of the Ophthalmological Societies of the following countries: Hungary, Yugo-Slavia, Italy, Egypt, Brazil, Mexico and Greece. He was an honorary member of the Oxford Ophthalmological Congress and a recipient of the Doyne Medal. A list of his publications contains 124 items, mostly in the German literature between 1900 and 1941. To the English-speaking world he is best known by his book on ophthalmic surgery, of which the second edition was published in Philadelphia in 1912. It had an extensive sale for some years in this country. In Austria and Germany the "Augenärtzliche Eingriffe" ran to five editions.

F. A. J.

CORRESPONDENCE

THE FINAL RESULTS OF SQUINT OPERATIONS, IN WHICH RESTORATION OF BINOCULAR SINGLE VISION WAS NOT EXPECTED

To the Editorial Committee of

THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—Dr. Stanworth is to be congratulated on this article which serves to emphasise the value of early and accurate operation in cases of strabismus in children.

He has not, however, perhaps sufficiently emphasised the importance of the age of onset of the condition. For instance, if a squint does not develop until after the age of three years, whatever the subsequent findings on the synoptophore, restoration of binocular single vision ought to be possible, provided that the visual acuity of each eye is approximately equal (or has been rendered so by means of occlusion) and provided that the visual axes are rendered parallel, or within a few degrees of parallelism, by means of accurate surgery. If there is a vertical deviation in addition to the horizontal deviation, this of course must be adequately overcome also.

Much time is often wasted arguing about the precise state of the binocular vision, when it should be appreciated that if a child has once possessed binocular single vision and has developed his binocular reflexes normally, it should be possible to restore these functions if proper conditions are provided.

The more difficult cases are those in which the squint dates from birth or from a very early age, but even in these cases it is often possible to obtain a functional cure by means of accurate surgery carried out within the first two or three years of life.

Yours faithfully,

T. KEITH LYLE.

42, CHARLES STREET, W.1
August 23, 1949.

TRAUMATIC OR "CONCUSSION" CHRONIC GLAUCOMA

To the Editorial Committee of

THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—I wish to refer to the carefully-written paper on the above subject by Mr. Arthur d'Ombrain in the August number of this journal (1949, **33**, 495).

The thesis that unilateral chronic glaucoma may be due to previous trauma appears to be founded mainly upon two facts:—

(1) the history of trauma involving an eye, *e.g.*, as a "black-eye," (2) the length of time during which the second eye has remained free from signs or symptoms. I venture to suggest that this is rather a flimsy structure on which to build an edifice so important from the medico-legal aspect. I would draw attention (1) to the fact that the three patients reported were males, and that it must be rather a rare event for a male to pass through life without receiving a "black-eye." (2) The period that elapsed with the patients under observation was 6, 3½ and less than 2 years respectively, since the discovery of chronic glaucoma. It must be the experience of many ophthalmic surgeons to have noted the onset of straight primary glaucoma in the second eye at a much longer interval after its discovery in the first, in patients under regular periodical examination.

Without going through the records of all my private cases of glaucoma, I recall two private patients in this category in whom the interval was 5 years and 10 years, the former male and the latter female. I have little doubt that the former would admit on enquiry to having had a blow on one or both eyes, but I should not on this account classify him as a case of "concussion" glaucoma.

I have no wish to dispute the value of Mr. d'Ombrain's argument. I do, however, feel that the great rarity of the occurrence to which he draws attention should be emphasised, chiefly on account of the medico-legal implications. My view is supported by the "brief and scattered allusions (in the literature) to the possibility of such a lesion" (p. 499).

Yours faithfully,

HUMPHREY NEAME.

149, HARLEY STREET, W.1
August 12, 1949.

NOTES

Prevention of Blindness in Mexico THE Society for the Prevention of Blindness in Mexico will be celebrating its 4th Biennial Congress from November 6 to November 12, 1949.

* * * *

University of Glasgow Department of Ophthalmology Autumn Term, 1949 DURING October a series of meetings will be held in the Department on Wednesdays at 8 p.m. The general arrangements will be similar to those of the series held last year. A discussion will follow the main paper. *October 5*, Dr. Geo. Leaf—"Biochemical Aspects of Methanol Poisoning"; *October 12*, Dr. W. O. G. Taylor—"Control of Clotting in Ophthalmology"; *October 19*, Dr. R. Leishman—"Tobacco Amblyopia"; *October 26*, Dr. A. Wright Thomson—"Gyrate Atrophy of the Choroid."

THE BRITISH JOURNAL
OF
OPHTHALMOLOGY

NOVEMBER, 1949

COMMUNICATIONS

VON HIPPEL-LINDAU DISEASE*
Clinical and Pathological Report of a Case

BY

I. C. MICHAELSON *and* J. HILL

GLASGOW

IT IS not often that an opportunity presents itself for the histological study of a case of von Hippel's disease; and it is even more unusual to combine this with microscopic examination of one of the tumours in the central nervous system, described by Lindau. The case here reported offers both opportunities, and may help to throw some light on the pathogenesis of the v. Hippel-Lindau complex.

The patient, a man aged 24 years, was seen for the first time at the Glasgow Eye Infirmary on March 22, 1948, complaining of defective vision in the right eye, and repeated attacks of epistaxis for a number of years. For one month

* Received for publication May 28, 1949.

there had been severe intermittent left occipital headache, especially severe in the mornings, and once or twice associated with projectile vomiting. Seven weeks before admission he had an attack of giddiness leading to collapse.

In the right eye (Fig. 1) the ophthalmoscope showed a large grey globular detachment of the retina in the lower nasal quadrant, and several smaller detachments above. The principal retinal vessels were much dilated and tortuous. There was diffuse white opacity of much of the detached retina. Transillumination

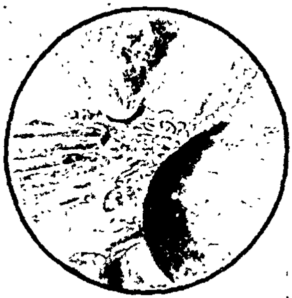


FIG. 1.

v. Hippel—Lindau disease. Ophthalmoscopic examination of right eye before excision. Extensive retinal detachment. Distension and tortuosity of vessels. New-built vessels. Gliosis.

gave an indefinite shadow in the lower area. The tension of the eye was normal. The fundus of the left eye was normal.

General examination revealed no abnormality of blood pressure, or of the circulatory, respiratory, gastro-intestinal or nervous systems. W.R. was negative. There were no cutaneous angiomata, and no X-ray evidence of intracranial disease.

The right eye was excised on April 16, and on April 21 he was transferred to the neuro-surgical unit at Killearn Hospital.

Operation (Dr. Schorstein) disclosed a cerebellar tumour, the removal of which was followed by deep X-ray therapy. The patient made an excellent recovery. The tumour was diagnosed as a haemangioblastoma.

PATHOLOGY

Serial sections of the retina of the right eye were cut in paraffin in the 12 to 6 o'clock meridian, and stained with haematoxylin and eosin, Mallory, van Gieson and Weigert's elastic tissue stain.

In a general survey the retina exhibits great distortion, variations in thickness, and degeneration of the retinal layers. At no part of the fundus is there a completely normal retina. In the least affected parts, about 5 mm. above and below the macula, there is destruction of the rods and cones and confusion of the nuclear and internuclear layers. In the more central area there is extensive destruction of the nuclear and ganglion cell layers, the retina for the most part consisting of coarse bands of neuroglia passing obliquely or anteroposteriorly through its whole thickness.

There are many *cysts* (Fig. 2) large and small, round and irregular in shape, empty or otherwise. The contents of the cysts consist of large cells with scanty pigment granules, apparently derivatives of the hexagonal pigment cells. There are so many gradations between the round, clearly defined cavities and the ragged fissures that it is difficult to say which are true cysts and which are the result of the tendency to cleavage of the retina along the lines of the glial framework.

FIG. 2.

Degenerate retina. A fibro-cellular septum which projects into a large cyst contains endothelial cells.

FIG. 3.

A large nodule, composed mainly of glial and endothelial cells Small vessels are forming. The nodule occupies the whole thickness of the retina. In the upper part of the photograph a neighbouring nodule has undergone hyalinisation of the matrix.

FIG. 4.

v. Hippel — Lindau Disease. Diffuse gliosis and multiplication of small vessels. Hyaline change in the matrix of the tumour tissue.

FIG. 5.

Two large vessels in the degenerate retina. The coats of the vessel walls are not distinguishable, and the wall of one vessel (vein?) contains several intra-mural vessels.

Dark clumps of *pigment cells* are deposited in irregular fashion, especially in the posterior part of the retina, but also as far forward as the nerve fibre layer. They often form dark deposits in the walls of vessels or cysts.

Pseudo-membranes of varying thickness are found attached to both anterior and posterior surfaces of the retina. At some points these are in continuity with

substantial homogeneous masses (hyaline?) in the retina, some of which contain blood vessels.

A striking feature of this part of the retina is the presence of fibro-cellular *nodules*, of varying size and situated in any or all of the layers (Fig. 3). There are also more diffuse patches of somewhat similar fibro-cellular structure (Fig. 4).

In sections just temporal to the disc the principal vessels are recognised as an upper and lower pair, corresponding with the normal superior and inferior temporal vessels. Both artery and vein are expanded and have thickened walls. In some parts there is lymphocytic infiltration of the wall. Here and there additional large vessels appear, probably produced by expansion of subsidiary branches. Large vessels have not only encroached on the deep and superficial layers, but at several points are seen to have perforated the anterior and the posterior limiting membranes.

Some vessels are seen which show little change from the normal histology, but in most there is not only thickening but also a varying degree of hyaline change.

One or two of the larger vessels show an incomplete differentiation of their coats; the walls contain some scattered endothelial cells, and here and there are intramural vessels, or *vasa vasorum,* similar to those described by Loewenstein (1947) (Fig. 5).

The gross changes so far described are largely degenerative, and do not in themselves offer any guide to the pathogenesis of the condition. For this we *have to turn to the nodular lesions already mentioned. It seems to be here that* we find a clue to the earliest stage in this tumour formation. The nodules vary greatly in size, the largest occupying the whole depth of the thickened retina

FIG. 6.

A cluster of endothelial cells, deep in the retina, resembles a giant-cell.

FIG. 7.

Another cluster of endothelial cells, in the anterior part of the retina, shows the formation of endothelium-lined vessels.

(Fig. 3). At a number of points we find clusters of endothelial cells, as small as 30μ in diameter, with a strong resemblance to giant-cells (Fig. 6). In some of these clusters clear vacuoles appear, lined with endothelium (now definitely blood-vessels) (Fig. 7). These increase in number and size, while the matrix in which *they are embedded increases in amount and is seen to be* composed of neuroglia together with endothelial cells.

These changes apparently represent a series of phases in the growth of the nodule; and a further change, which would appear to be the next stage in the process, is the gradual hyalinisation of the matrix. This begins in the central

part (Fig. 8) and extends gradually through the rest of the nodule, until the matrix loses its fibro-cellular character, and the vessels are seen to be embedded in a homogeneous waxy-looking mass (Fig. 9) which stains faintly red with eosin, blue with Mallory, and crimson with van Gieson. With Mallory a certain fibrillary structure is indicated.

A similar series of changes takes place more diffusely in this part of the retina. We have noted that much of the degenerative retina is composed of coarse bands of glial tissue. These are associated here and there with endothelial cells which do not group themselves in nodular form. This "gliosis" gives place to a hyaline material, sometimes with, and sometimes without enclosed capillary vessels.

In all these parts, both in the nodules and in the intervening tissue, the proportion of vessels to matrix varies a good deal. Sometimes large vessels join up to form a cavernous plexus, elsewhere the vessels may be few and of capillary structure, buried in a mass of "hyaline" tissue. Here and there we find a very small nodule of the endotheliomatous tissue in the wall of a large cyst, or in a

FIG. 8.

A large nodule, about 250μ in diameter, in the posterior part of the retina. It is full of small vessels. The matrix is becoming hyaline.

FIG. 9.

A large angiomatous nodule in which the vessel walls and the supporting matrix are almost completely hyaline.

septum of connective tissue projecting into the cyst (Fig. 2). This may have some relation to the haemangiomatous cysts in other organs discovered in Lindau's cases.

The aforementioned hyaline changes, which are a pronounced feature of most of the sections, are of interest, but their significance is not clear. The hyaline material appears:—(1) as a result of the progressive change in the fibro-cellular matrix of the nodules, as well as in the intervening tissues (Fig. 8); (2) as a result of a pathological change in the thickened walls of the retinal vessels, both small and large (Fig. 9); and (3) as hyaline masses at all depths in the retina and on its anterior surface, some of which contain a few small vessels while others are completely avascular (Fig. 4). It may be taken as a degenerative change in the overgrown neuroglial tissue of the retina, probably the latest phase in the growth of the retinal tumour.

THE CEREBELLAR TUMOUR

The histological character of the portion of the cerebellar tumour available to us differs from that of the retinal growth, (1) in the absence of nodular formations; (2) in the absence of the degenerative changes, such as cyst-formation,

gliosis and hyalinisation, as seen in the retinal tumour. Here and there we find clusters of unorganised endothelial cells resembling giant-cells, some of which contain one or two small vascular channels lined with endothelium, and the tumour tissue in general consists of a light matrix of endothelial and supporting cells containing many blood-channels of widely varying size, lined with flattened or almost cubical endothelial cells. In some parts a free inter-communication between neighbouring vessels gives the tumour a cavernous character.

Incidentally, sections from a case of cavernous angioma of the eyelid, for which we are indebted to Professor A. Loewenstein, show appearances almost identical with those in Fig. 8.

Comment

The problem of the isolation and identification of the initial lesion is one which is common to all retinal diseases of "massive exudative" type; for the eyes in these cases are seldom submitted to pathological examination until marked secondary changes have occurred. In this country the first important contribution to our knowledge of the disease was that of Collins (1894), who had the opportunity of studying the histology of an eye which had been clinically examined and described two years earlier by Wood (1892), and subsequently of examining both eyes of this patient's sister. In each of these eyes there was complete retinal detachment and advanced degenerative changes, but the central retinal tumour had the structure of a capillary naevus, the matrix of which contained many scattered cells apparently endothelial in character. Cystic spaces abounded in the tumour and in the retina generally, and Collins described the condition as a capillary naevus of the retina with cystic degeneration.

v. Hippel discussed the condition in 1895 from the clinical, and in 1911 from the pathological aspect, and earned for it the name of von Hippel's disease. Coats (1908) described the disease among the forms of retinal disease with massive exudate, and supported the view of Collins, v. Hippel and Czermak that it must be considered as a true vascular new-formation. Lindau (1926) established the close association of v. Hippel's disease with the haemangiomatous cysts of the cerebellum and other organs described by himself. In the subsequent literature on the pathology of v. Hippel's disease emphasis has been placed on the presence of endothelial cells throughout the retinal tumour.

Two views are expressed regarding the pathogenesis of the condition, namely; (1) that the growth is primarily a gliosis which undergoes a secondary vascularisation, and (2) that the vessel formation is primary and the gliosis a secondary reaction. Meller and Marburg (1928) and others who support the first view point out that the glial formation is out of all proportion to the vessels, which may be very scanty. They have also found a massive gliosis without any vascularisation or endothelial cells.

They emphasise that glial masses may be found in the deeper non-vascular layers of the retina: but we are bound to admit that there may be not only persistence and proliferation, but also displacement, of the embryonic cells of origin. One argument in favour of the primarily vascular nature of the growth is that the vessels in the tumour nodules appear to be independent of the local circulation, and have no resemblance to the vascular pattern of the retina. Again Lindau (1936), Paton (1929) and others have examined cases in which the tumour contained no glial tissue, and clinically the vascular aspect of the tumour may be evident for some time before gliosis appears.

The occurrence, in the present case, of clusters of endothelial cells without vessels is significant, and supports the view that the lesion is a haemangio-endothelioma or haemangio-blastoma. The ophthalmoscopic and microscopic features of the case bring it into line with the cases of Lindau (1927), Paton, Williamson-Noble and Greenfield (1929), Sladden (1930) and A. E. Macdonald (1948), which are among the few cases in which the complete v. Hippel-Lindau complex was present and both microscopic and ophthalmoscopic examinations were obtained. The feature common to all these cases is that the actual tumour is composed largely of endothelial cells, some of which proceed to form rudimentary blood vessels. The relative abundance of endothelial cells, blood vessels and glial tissue varies from case to case and even in different parts of the same retina.

From the findings in the present case, it would seem that the initial pathological unit is a cluster of endothelial cells destined to form a vascular endothelium, but persisting in a more or less embryonic state, proliferating and invading the avascular layers of the retina. The overgrowth of neuroglia, the formation of retinal cysts, the widespread hyaline change and the general disorganisation of the retina must be looked upon as secondary. It is evident that the vessels of the angioma are not formed by budding from mature retinal vessels but by the pursuit, by the endothelial cells, of their destined function of vessel-formation. The tumour shows no signs of malignancy, but the eye may be destroyed by the occurrence of haemorrhage, glaucoma or detachment of the retina.

Summary and conclusion

The case is described of a young man who suffered from angiomatosis retinae (v. Hippel) accompanied by cerebellar haemangioma (Lindau). The affected eye was excised and subsequently the cerebellar tumour was removed. Both were subjected to microscopic examination.

The cerebellar tumour consisted of a soft fibro-cellular mass, containing many clear endothelial-lined spaces, some cystic, others vascular. Unorganised endothelial cells were diffused through the matrix of the tumour.

In the retina, which was grossly disorganised, there were

(1) Clusters of endothelial cells, some of the latter grouping themselves to form capillary vessels. The endothelial cell cluster seems to be the pathological unit.

(2) Larger clusters or nodules, some of them filling the whole thickness of the retina, and consisting of a fibro-cellular (glial) matrix containing new vessels of varying size as well as unorganised endothelium.

(3) A hyaline change, first of all at the centre of the nodules, but later converting the whole nodule to a hyaline mass.

(4) Similar changes in a more diffuse form, predominantly a gliosis.

(5) Cystic, pigmentary and other forms of degeneration.

The findings support the view that the vessel-formation is primary and the gliosis of the retina secondary.

The tumour cells are not derived from the large mature retinal vessels. It is probable that they are derived from the capillary endothelium, or rather from the anlage of such endothelium. Such an anlage develops by budding from the vascular endothelium confined at an early embryonic stage to the optic nerve region, and does not develop from neural cells.

The tumour is a true haemangio-blastoma or haemangio-endothelioma.

We would express our thanks to Prof. A. J. Ballantyne for his close interest in this case and his help in working-out the histology.

Fig. 1 is from a coloured drawing of the fundus by Mr. Gabriel Donald.

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ANTIHISTAMINES IN OPHTHALMOLOGY*

BY

LEWIS NÉMETH

HISTAMINE plays an important rôle in the mechanism of allergy or hypersensitive diseases of the constitution. This substance is to be found preformed as histidin in the cells; by the antigen-antibody reaction which acts on the cell-walls, histamine is released and thereafter produces the allergic symptoms. This classically simple interpretation of the allergic process was renewed lately in a more complicated and theoretically preferable form. Several authors believe the allergic reaction to be the result of allergen activating the preformed reagin contained in the cells, and this as catalyser releases a great quantity of H. substance. These H. substances, of which histamine is the most important, produce the symptoms which can be observed clinically. These H. substances which produce the allergic symptoms are products of the irritation of the cells caused by the allergen reaction which starts those well-known changes in the small veins — namely, increase in diameter and permeability.

This short sketch of the allergic mechanism shows the need for variability in the treatment of allergic diseases. Anti-allergic treatment can be specific when we try to prevent the real cause, the meeting of allergen-reagin, by preventing access of the specific allergen to the system. In other cases we try to exclude the reagin by desensitization. This specific treatment is rather complicated, and demands special technique. Therefore simpler methods have been sought in the treatment of allergic diseases, including those of ocular origin. Such were found when the significance of the H. substances in the causation of allergic diseases became known, and it seemed desirable to eliminate these H. substances. Such treatment was not specific, and had formerly been tried in utilising the fermentation of histamine to alleviate allergic diseases. Long ago we used "Torantil" for this purpose. This proteid substance, derived from the mucuous membrane of the intestines, can inactivate histamine and sometimes restrains allergic manifestations. One tablet was prescribed three times daily, but it often fails in practice notwithstanding its theoretical value.

The difficulty of searching for a specific antigen and the technical obstacles to be overcome before it can act as a desensitiser induced me some years ago to use histamine to lessen or abolish constitutional hypersensitivity. The diagnostic value of the histamine

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* Received for publication March 1, 1949.

From the II Ophthalmological Clinic of the Pázmány Péter University in Budapest. Director: Professor Tibor Nonay.

skin-test which I formerly recommended was also an aid in deciding the line of treatment. When the histamine skin-test was positive, I tried to lessen hypersensitivity in allergic eye-diseases by injecting histamine under the skin. I noted obvious and lasting results several times, and this treatment is often used by us in allergic eye-diseases. It is uncertain how histamine hypodermically administered in small, increasing doses, produces a favourable result in allergic eye-diseases. Perhaps increasing doses of histamine accustom the constitution to endogenous histamine effects, such as may arise in an allergic disease. The beneficial effect of histamine introduced in increasing quantities is based not so much on the production of antibodies, as on the outpouring of adrenalin thereby provoked. Histamine can produce the formation of antibodies only in the form of complex antigen, so that presumably the good effect of histamine treatment is due to adrenalin, though histamine subcutaneously linked with tissue-protein plays the part of a complex antigen.

Recent researches have produced synthetic substances which can inhibit histamine. Amidst the numerous experimentally tested drugs are several so-called anti-allergic drugs used clinically with success. The basis of the knowledge is the protective effect of certain phenol-ethers against histamine intoxication. Staub and Bovet in 1937, stated that fatal anaphylactic shock of a hypersensitised guinea-pig can be avoided by thymoxyethyldiæthylamin 929 F, but this substance proved toxic. Further research resulted in such synthetic anti-histamines as antergan, neo-antergan, antistin, benadryl and pyri-benzamin. All of them neutralise histamine, abolish or minimise allergic manifestations and are almost non-toxic. Antergan medicinally used in France has caused death, but neo-antergan is less toxic. The daily dose of each is 0.6 gm., benadryl and pyridenzamin are produced in America, and the dose of each is 50 mgm. by the mouth. Favourable results were obtained in allergic diseases such as urticaria, œdema of Quincke, hay-fever, vasomotor rhinitis and pruritus. Dean recently described a case in which fever due to penicillin treatment, dyspnœa and general urticaria ceased a few hours after administering 130 mgm. of benadryl. Its accessory effects, such as fainting, palpitation and nervousness, are mild.

Rosso considers ocular manifestations in the intermenstrual period of certain women as allergic. He believes that in this period there is a surplus of histamine-like substances. These disturb the biochemical equilibrium of the aqueous humour and conduce to various eye diseases. Hence we cannot always obtain good results from hormonal treatment. On this basis Rosso tried to utilise dimethyl-amino-ethyl-benzylamidin-hydrochloride, the antagonist of histamine

as an anti-histamine substance. Intermenstrual episcleritis and uveitis reacted well so did conjunctival, eye-lid and other manifestations. He administered the drug orally, intravenously in a 2·0 per cent. solution, and as drops in 0·5 per cent. solution. We have no personal experience of these drugs.

The Ciba factory kindly allowed us to test their antihistamine product antistin, and we found it effective. It is a derivative of imidazolin of the priscol-privin series. Meier and Bucher verified by animal experiments in 1946 its antagonistic action upon histamine. It is uncertain whether this action is direct desensitisation of histamine or whether it can be otherwise explained, but at any rate we can expect results from antistin treatment when organic changes in the allergic constitution have not yet developed. Its favourable effect can be observed in anaphylactic symptoms and allergic diseases, as well as in diseases caused by allergic-inflammatory factors, *e.g.*, nephritis. This effect was also described in the Hungarian literature for internal medicine. This drug was employed in many different diseases with striking success. It can be used in tablets of 100 mgm. orally, or by intramuscular injection. The average daily dose is 300 mgm. but more can be given without provoking toxic effects. Ophthalmologists are especially interested in the solution which can be applied as drops. The watery solution contains 0·5 per cent. antistin and 0·025 per cent. privin. Privin, being an imidazolin derivative checks swelling of the mucous membrane, and by contracting the veins even more than does adrenalin, it potentiates the antistin effect. We observed the remonstrable effect of antistin-privin drops in many different allergic eye-diseases, as in the following case.

1. H. G., a 60-year-old man, complained that his right upper eye-lid swelled suddenly and became irritable though not painful. His right eye was watery. On the previous night he had eaten eggs. On the right upper eye-lid there was a typical oedema of Quincke, and on the same side allergic conjunctivitis. After half-an-haur poulticing with a tampon soaked in antistin-privin solution, together with instillation of drops, he went away cured. It was not possible to determine the aetiology. Histamine skin-test was positive.

2. Sz. K., a 35-year-old man, gave a history of eczema on the scrotum and both legs in 1942. In Spring, 1943, eczema appeared on the right ear. He was treated with his own blood-serum, autovaccination from his tonsils, Castellani solution. A week ago his right eye became inflamed, and he was elsewhere given noviform ointment and targesin solution to use at home. On examination his right eye-lids were greatly swollen by involvement in the moist eczema. The inflamed conjunctiva showed increased sensitivity, as corroborated by the presence of eosinophil cells in the conjunctival sac. The histamine skin-test was strongly positive. After three days of treatment with antistin instillation and antistin tablets three times daily by mouth, the skin of the pale eye-lids peeled in scales, the conjunctiva whitened, and secretion ceased. Those who have treated such eye-diseases know, that, with ordinary therapeutic measures, resolution takes 8-10 days.

3. R. H., male, 65 years, had been treated as an out-patient for 11 months for subacute allergic conjunctivitis. It was not possible to discover the origin of the malady but he said it developed after heavy sweating from strenous physical work. In spring he usually had a cold. The blood picture was normal, and the histamine-test positive. Before the administration of antistin he had been unsuccessfully

treated with various drugs. His discomfort ceased after a week's instillation with antistin once daily. In 10 days he completely recovered, and there have been no relapses in the past six months.

4. Cs. L., a 40 year-old woman, had been treated for similar trouble in her right eye at an insurance hospital for six months. Various drops and milk-injections afforded no benefit. She stated that she was cured by penicillin ointment in another hospital, but three months after her recovery fresh inflammation arose in her right eye. She showed marked photophobia, and there were 8-10 superficial punctate infiltrations scattered over the cornea. This superficial keratitis, of which the cause was obscure, was probably a form of hypersensitivity, and it cleared after instillation of antistin once daily for three days. The histamine skin-test was strongly positive in this case also.

We have observed rapid benefit from antistin treatment in cases of blepharitis due to penicillin hypersensitivity, and in conjunctival diseases. The prolonged use of sulphonamides and antibiotics can sensitize the organism. Allergic symptoms arising from such causes are favourably influenced by antistin.

The same benefit ensued in a man with conjunctivitis accompanying widespread dermatitis provoked by a mercury skin ointment applied once only. Antistin instilled once daily for 3-4 days relieved him of his eye-symptoms, and also abolished eye-symptoms due to sensitization by pilocarpin.

We also observed beneficial results in the conjunctivits of hay fever. The patient rapidly lost his discomfort. Success was also obtained in spring-catarrh treated with antistin, orally or in drops. Symptoms ceased or were relieved, though the objective picture scarcely changed.

Györffy and Kahán tried antistin in patients complaining of irritation from the wearing of contact-glasses. They supposed that over sensitiveness to the contact-glass, irritating the cornea, produced in some people an increase of histamine. More than half of these patients could wear the contact glass for a longer time after previous instillation of antistin, than they could without antistin.

Subsequently we saw favourable results in the oedema of Quincke, acute and subacute conjunctivitis accompanied by allergic dermatitis, eczema, allergic conjunctivitis including that of hay-fever, spring-catarrh and superficial keratitis. Antistin given orally checked the reactions of hypersensitivity caused by penicillin,

Finally, we must mention episcleritis, iridocyclitis and uveitis of focal origin. It is supposed that noxious foci produce antigens, which cause allergic outbursts, *e.g.*, iridocyclitis, by sensitizing the constitution. The ideal solution would be to stop the production of antigen by removal of the focus. Belated removal of the focus does not, however, always prove beneficial owing to an increase of parallergy. This explains frequent relapses even after removal of the focus. In such cases peroral treatment by antistin seems theoretically sound, but success in a few cases does not permit far-reaching assumptions, and further investigations are required. Bourquin relates similar observations. With this same object we used the 5497/3 nr. anti-allergicum produced by the Hoftmann-la Roche factory. This drug is available in America under the name

of Tephorin. We used it successfully for cases of chronic uveitis, in which moderate increase of monocytes denoted hypersensitivity. Good results were also obtained in some cases of spring-catarrh, though one patient complained of insomnia. He was taking 3-6 tablets a day.

In conclusion we can assert that the discovery of synthetic antihistamine substances offer a new method of treatment for allergic diseases. Such treatment is at once palliative and symptomatic. These histaminolytic substances are beneficial in ocular disease, and our results with antistin encourage us to advise these substances for trial.

Summary

The mechanism of allergy and various forms of allergic treatment are reviewed. Specific treatment is not always possible. The knowledge of H. substances opens up new methods of treatment. The notion of rendering substances such as histamime ineffective has been under consideration. One may try to accustom the constitution to histamine or to desensitise the organism thereto. For diagnostic purposes in eye diseases, I advise the histamine skin-test, and note the good results obtained in allergic eye diseases by small subcutaneous injections of histamine. The latest anti-histamine drugs can inhibit histamine, and combat allergic eye diseases. Experience with antistin produced by Ciba are reviewed. Good results were seen in the oedema of Quincke, acute and subacute conjunctivitis associated with allergic dermatitis, eczema, allergic conjunctivitis, hay-fever, spring-catarrh and superficial keratitis. Antistin favourably influenced the hypersensitivity reactions caused by penicillin. In all these conditions it was applied locally, but in the treatment of episcleritis and uveitis of focal origin antistin given by the mouth often proved beneficial. In view of the good results obtained these antihistamine substances can be recommended for trial by ophthalmologists.

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SOME WAR TIME STATISTICS*

BY

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THE recent publication of a Statistical Report on the Health of the Army from 1943 to 1945[1] has provided the military ophthalmologist with a wealth of information. This work presents some of the ophthalmic problems peculiar to troops stationed in the United Kingdom, and outlines some of those encountered during the campaigns of Europe and Africa. At first sight such statistics would appear to have only a limited value in this atomic age, but it must be remembered that the basic morbidity rates for ophthalmic disease amongst British soldiers will remain virtually unaltered in all future wars. Atom bombs, on the other hand, will affect the casualty rates considerably, and may even align the figures for ophthalmic injury in the 1939-1945 war with those of campaigns of a bow-and-arrow era.

European armies by 1939 had achieved only relatively slight increase in efficacy of the explosives and projectiles used, compared with those employed in the wars of the previous half-century. Thus the histories of these conflicts gave the military oculist some rule-of-thumb data to go by. Some two-and-a-half per cent. of the total battle casualties would thus be expected to have sustained wounds of the eye and orbit. If, however, wounds of the head and neck region were aggregated, these might even prove responsible for up to ten per cent. of the injured that were evacuated from the battle-field. The ophthalmologist expected, and indeed soon learned by his own experience that, if a soldier were to be hospitalised for any ophthalmic lesion, then that man's unit would be lucky if it received him back under a month. It would be suspected that ophthalmic disease was only responsible for about one per cent. of the total sickness amongst British troops in most parts of the world, and the ophthalmologist would find that about five per cent. of the personnel of a fighting division and from ten to fifteen per cent. of personnel of the L. of C. troops would need spectacles to render them militarily efficient. It is interesting to compare these pre-conceptions with the figures for disease and injury given by statisticians.

OPHTHALMIC MORBIDITY IN THE UNITED KINGDOM

The report provides us with the startling generalisation that the overall sickness rate in the United Kingdom during 1943 was such

* Date submitted for publication, May 27, 1949

that every soldier might well have spent one day of that year in reception stations, and eleven days in hospital or convalescent depots. It is interesting to note that two-thirds of all the military cases of ophthalmic disease were treated in the Army's own hospitals, while the other third were treated in civilian hospitals under the Emergency Medical Scheme. Cases suffering from eye disease in 1943 comprised some two per cent. of the population of military hospitals.

The relative casualty rate — that is, the percentage of eye disease amongst all persons lying in hospitals either for reason of sickness or injury — proved to be 1·4 for all male other ranks and 0·8 for members of the Army women's services (A.T.S.). On exclusion of the persons in hospital because of injury, we obtain the relative morbidity rate for ophthalmic disease, and this worked out as 1·0 per cent. for the male other ranks, and remained, as might be expected, at 0·8 per cent. for the A.T.S. The mean duration of stay in hospital for cases of eye disease was found to average out as 28·4 days for male other ranks and 24·3 days for the A.T.S.

OPHTHALMIC MORBIDITY IN THE MIDDLE EAST

Since the days of the Bible the history of war in the Middle East has abounded with descriptions of epidemics of the ophthalmias amongst the armies engaged. The following figures are therefore particularly instructive: The relative casualty rate in 1943 amongst hospitalised other ranks was 1·87 per cent. for ophthalmic lesions. This was therefore only an increase of approximately a third above those hospitalised in the United Kingdom. The relative casualty rate for the officer hospital population proved only to be 0·72 per cent.

Further analysis in the report showed that conjunctivitis accounted for 0·74 per cent. in 1943 and 0·73 per cent. in 1944 of all lesions amongst the other rank hospital population. The diagnosis of keratitis in 1943 covered 0·50 per cent. of all lesions and in 1944 some 0·49 per cent. The officer hospital population suffered far less from conjunctivitis or keratitis. Thus the conjunctivitis incidence in 1943 amongst officers was 0·29 per cent. of the total lesions and keratitis 0·25 per cent. In 1944 the morbidity rate was 0·25 per cent. for conjunctivitis and 0·19 per cent. for keratitis.

The Middle East ceased to be the theatre of large scale operations in the autumn of 1943, and the consequent lessening of urgency in the need to return men to the front is reflected in the increased time that eye cases now spent in hospital. The average time in hospital for the conjunctivitis cases rose from 18·6 days in 1943 to 22·5 days in 1944, and for the keratitis cases from 27·9 days in 1943 to 32·9 days in 1944. The Middle East Force at this time was a polygot army,

and some interest lies in the variety in the incidence of ophthalmic lesions amongst troops of different races. The relative casualty rate for United Kingdom troops with ophthalmic disease in hospital worked out at 1·6 per cent. for Dominion troops at 1·8 per cent. for British African troops at 1·7 per cent. whilst for Indian troops it was 5·6 per cent. That the Indian troops were thus badly affected was probably due to the fact that since 1930 recruiting regulations had been relaxed to permit of the enlistment of men with "healed trachoma." The incidence of trachoma amongst Indian troops is held by some authorities to be almost one hundred per cent.

SEASONAL INCIDENCE OF CONJUNCTIVITIS AND KERATITIS IN THE MIDDLE EAST

This portion of the earth's surface is regularly plagued at certain times of the year with heat, dust and flies. The two graphs show that the highest incidence of conjuntivitis and keratitis do not directly coincide with the main "Khamseen" and fly-breeding

ONE HUNDRED CASES OF CONJUNCTIVITIS

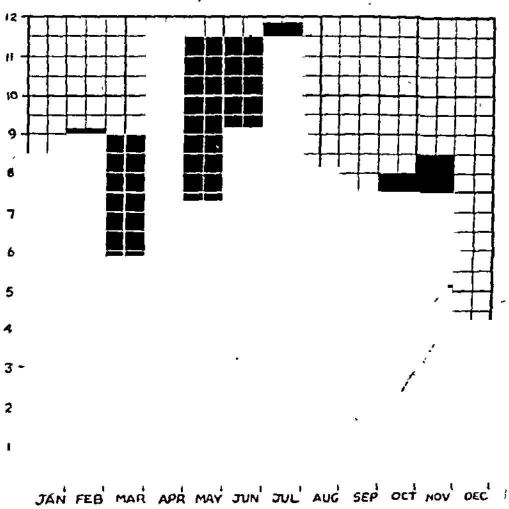

FIG. 1.

periods. Among the various units the R.A.O.C. suffered most from conjunctivitis. This was to be expected from the nature of their duties, of necessity carried out with little protection from the elements in large sandy Ordnance Depots.

ONE HUNDRED CASES OF KERATITIS

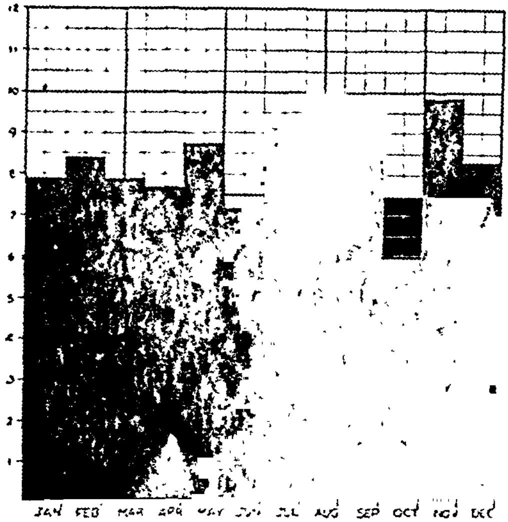

FIG. 2.

OPHTHALMIC MORBIDITY IN THE CENTRAL MEDITERRANEAN FORCE

The report divides the ophthalmic lesions incurred in this theatre of war into 49·9 per cent. conjunctivitis, 25·5 per cent. keratitis, and other ophthalmic disease 24·6 per cent. The relative casualty rate in 1944 was worked out at 1·1 per cent. for other ranks, and 0·4 per cent. for officers. During the whole period under review the C.M. Force was engaged in active operations against the enemy in Italy. The mean duration of stay in hospital proved to be 22·4 days, ranging from an average of 18.7 days for the conjunctivitis cases to 30·1 days for those of keratitis.

DISCHARGES FROM THE ARMY

Men suffering from intractable ophthalmic lesions or with vision below the requisite standards for service were generally made to take their discharge from the Army in the United Kingdom. Thus during 1943 cases of eye diseases constituted some 2·2 per cent. of the total discharges from the Army for sickness or for injury. In 1944 this percentage had fallen to 1·55 per cent., and again in 1945 to 1·15 per cent. Corresponding figures for the A.T.S. worked out at 1·4 per cent. in 1943, 0·9 per cent. in 1944 and 0·7 per cent. in 1945. Thus the effects of lowering the minimal visual standards in the last years of the war are reflected in the change in these

figures. From another standpoint it can be said that, for every 100,000 male other ranks in the Army in 1943, some 48·3 had to be discharged for "eye-disease." In 1944 this had fallen to 39·4 per 100,000, but there was a slight rise again in 1945 to 40·6 men per 100,000 due to shrinkage of the army at the end of hostilities. An equal strength of A.T.S. would have lost 28·6 women in 1943, falling to 18·6 in 1944 and showing a very minor increase to 18·7 in 1945.

INVALIDING DISABILITIES AMONGST PRISONERS OF WAR

The recording of invaliding disabilities amongst prisoners of war, and especially those returned from the Far East, showed up one real difficulty in the application of statistical methods to medicine. The problem lies in the separation of the so-called primary and secondary invaliding disabilities. For example a P/W from the Far East had often contracted malaria, dysentery, beri-beri and an "optic neuritis." The invaliding medical officer would therefore have some difficulty in recording what constituted the "primary" disabilities, when his examination took place some years after the onset of these several diseases. Thus the allocation of the primary disability often became merely an expression of the medical officer's personal opinion derived from a vague clinical history.

In the statistical report the term "optical neuritis" was made to include retro-bulbar neuritis and optic atrophy. Other ophthalmic evidence of nutritional amblyopia was duly recorded as "defects of the field of vision." So the recorded primary disabilities amongst Far Eastern Ps./W. gave some 5½ per cent. as having incurred optic neuritis and a further 2 per cent. as showing defects of the field of vision. As soon as the secondary disabilities were taken into account, then the percentage of those discharged with either optic neuritis or defects of the field of vision rose to 11 per cent. of the total. There is an interesting comment that, at the time of their discharge from the Army, 25 per cent. of the men still showed effects of nutritional deficiency.

The following table gives an excellent comparison of the discharge rates for primary disabilities of the eyes.

Diagnosis	*Non-Prisoners*	*P.s/W. Europe*	*P.s/W. Far East*
Defects of the Field of Vision	0·3 per cent.	0·2 per cent.	2·0 per cent.
Optic Neuritis	0·1 per cent.	0·1 per cent.	5·6 per cent.

OPHTHALMIC BATTLE-CASUALTIES AND BATTLE-ACCIDENTS

The term battle-casualties is in common usage, but the term battle-accident may require some elaboration. It is employed to categorise the men who are indirectly injured by the enemy. Thus

the man may have sprung a booby-trap laid by the enemy some months before; or, for example, by the faulty handling of his own weapons in the field, the soldier may have detonated his own hand-grenades, although not in the presence of the enemy. "Battle-accident" therefore covers most of the accidents which might happen to the soldier as he carries out his calling in the field, except those caused by wilful negligence.

The report includes interesting statistics mainly obtained from the records of the North African campaigns. In that fighting, the rôle of the specialist surgical units in the field was such that, from their returns, it was possible to make a classification of wounds on an approximately anatomical basis of sites of injury. In the Normandy landings, a regional classification for wounds came into use in the place of the Neuro-surgical, Facio-Maxillary, Ophthalmic, etc., method used in the earlier campaigns. This regional method is probably the most logical way to record casualties, because wounds are often multiple, and their distribution often crosses the anatomical lines of demarcation, but, as will be seen later, figures obtained from casualties suffering from wounds of the head and neck region are unsatisfactory when the types of wounds of the eye have to be discussed.

The North African casualties were analysed for three separate two-month periods of intensive battle-fighting as under:—

Battle	*Period*	*Army Engaged*
Knightsbridge	May-June, 1942	VIII Army
El Alamein II	Oct.-Nov., 1942	VIII Army
Tunisia	Dec., 1942-Jan., 1943	I Army

In the three battle-periods above, wounds of the head, face or eyes were responsible for 12-17 per cent. of the total casualties.

Battle	*Neuro-surgical cases*	*Facio-Maxillary cases*	*Ophthalmic cases*
Knightsbridge	5·3 per cent.	4·3 per cent.	2·2 per cent.
El Alamein II	4·9 per cent.	7·0 per cent.	2·7 per cent.
Tunisia	9·5 per cent.	5·5 per cent.	1·6 per cent.

There were many casualties during all these three periods not strictly due to direct enemy action, *i.e.*, as later described, "battle-accidents." Thus some fifty per cent. of the Knightsbridge cases were battle-accidents forty-five per cent. at El Alamein II, and forty-eight per cent. in Tunisia.

When the casualties from the June-July Normandy landings in

1944 were analysed, the report states that only 15 per cent. of the campaign injuries were held not to be due to direct enemy action. Considering that a large proportion of the troops in the spearhead of the attack were the same men who had participated in the Middle East campaigns, it would seem that this point merely emphasizes the more generous method of recording a man's injuries.

The fighting troops in the North African campaigns were generally carried into battle in armoured or unarmoured petrol-driven vehicles. When hit in a vital part these vehicles would "brew-up," as the current expression described it. Therefore among the ophthalmic casualties there would be a large number of burns of the globe and adnexa. Among the total ophthalmic casualties at the Knightsbridge battle there were 5·1 per cent. burns cases, at El Alamein II some 4·8 per cent. and in Tunisia (where there were many tank casualties) some 7·7 per cent.

The report states that a very high proportion of the ophthalmic casualties were eventually returned to duty in the same theatre of operations. Thus from the Knightsbridge battle some 79·7 per cent. from El Alamein II some 77 per cent. and from the Tunisia fighting 66·7 per cent. were returned to duty in North Africa. Such figures, however, must be treated with caution, as they do not give any indication of the man's final visual efficiency, nor of the employments for which he was finally fit. For example, most of the North African theatre oculists will agree that very few infantrymen who had sustained a penetrating wound of the globe were ever fit for front-line service again, although they might be employable at the base, or on the lines of communication.

The report also makes mention of the remarkable consistency in distribution of the wounds of different parts of the body in all four campaigns. In Normandy some twelve per cent. of the total casualties were found to have suffered from wounds of the head and neck region. Of these, some 13·7 per cent. were *lethal*, death occurring during evacuation through medical units; 21·6 per cent. were *severe*, and prolonged hospitalisation of the men resulted; 42·3 per cent. were *medium*, and in these cases only short hospitalisation was necessary; 22·4 per cent. were *trivial*, so that, after treatment in the forward medical units, the men were returned to their units.

Single as opposed to multiple wounds of the head and neck region were grouped in the report as superficial 10·4 per cent.; flesh 70·9 per cent.; bone 12·6 per cent.; and burns 3·3 per cent., while concussion was only 2·7 per cent. This emphatically did not tally with the experience of most ophthalmologists, who accepted that eye-wounds due to blast as opposed to those from direct trauma by a projectile might form up to forty per cent. of the injuries of the

globe. Here is an instance in which the regional method of wound classification has its limitations.

It was interesting to read that the infantry sustained up to 80 per cent. of the mortar wounds but only some 50 per cent. of the mine wounds. The supporting troops were affected most by mine or bomb wounds, and it was also notable that half the wounded artillery men had been injured by the enemy's counter-battery fire.

SPECTACLES AND THE SOLDIER

As long ago as 1915, when the general introduction of spectacles into the Army was being carried out, it was estimated that five per cent. of every fighting division would need spectacles to make them militarily effective. This estimate was found valuable in the recent war. Some American statistics in respect of their draft (recruits) published in 1944 showed that 5·5 per cent. of the men enlisted had vision in the one eye of 6/18 or less[2]. A survey of British recruits in 1946/1947 gave a figure of 8·8 per cent. of the recruit intake as having vision of 6/18 or less in one eye[3]. Recently when recruits for the line of communication troops were examined, out of some eight thousand men some fifteen per cent. were found to need glasses. These would be men of slightly lower physical capacity than the fighting troops in a division. Under the Pulheems system of classification, wherein ophthalmic lesions give alteration of the P. rating (Physique), some 5 per cent. of these men were below P.2 (the normal). 298 men were placed in the P.3 rating, which is the "strabismus" rating.

Summary

(1) The figures for ophthalmic injury and disease quoted in the Statistical Report on the Health of the Army, 1943-45, agree in the main with the expectations of military ophthalmologists.

(2) The ophthalmic morbidity amongst the soldier population at home and abroad will not markedly alter in future wars, and it is to be hoped that statistics of this nature will not have been forgotten by the time of the next conflict.

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THE EFFECT OF HYALURONIDASE INJECTION ON THE VITREOUS HUMOUR OF THE RABBIT*

BY

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THE effect of hyaluronidase injections on the slit-lamp appearance and the composition of the vitreous humour of the rabbit has been examined. The purpose of the experiments has been to see whether disaggregation of hyaluronic acid from a viscous to a non-viscous form in the vitreous humour is a permanent change and whether any visible change persists as a result of hyaluronidase action. Very little is known of the production or fate of hyaluronic acid, either in the eye or in other fluids and tissues of the body, such as synovial fluid, skin, or Wharton's jelly, where it also occurs. Meyer (1947) has suggested that there is a circulation of hyaluronic acid in the eye, the viscous hyaluronic acid of the vitreous humour being disaggregated and removed through the normal exit channels. Presumably this is a very slow process in the normal eye and we do not know whether complete disaggregation of the vitreous hyaluronic acid, such as might take place under pathological conditions, can ever be reversed. Nor has any clinical change been correlated with such breakdown. Aggregated hyaluronic acid is the viscous material that contributes to the turgor of the vitreous humour and its loss—if irreversible—might possibly lead to considerable changes in the state of the vitreous body.

von Sallmann (1948) has briefly described the effect of injections of hyaluronidase on the vitreous humour of the rabbit. He found that the enzyme caused a considerable inflammatory response and considered its use too dangerous for clinical purposes. In the experiments reported here the eyes have been watched for nearly a year after injection of hyaluronidase to see if permanent change occurred and the vitreous humours have been analysed to see whether the chemical changes could be correlated with any clinical change. The eyes were examined with the slit-lamp and ophthalmoscope, and the composition of the vitreous humour, sometimes also of the aqueous humour, was determined when the animal was killed. In a few animals the effect of hyaluronidase on intra-ocular pressure was noted. The state of aggregation of hyaluronic acid was judged by the type of mucin

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clot it gave in acid acetone. The enzyme system hyaluronidase causes a rapid disaggregation followed by a slow hydrolysis of hyaluronic acid. The primary change only has been studied, as this seemed the most important relative to vitreous humour structure. Disaggregation can be followed either by following the change in the type of mucin clot produced by acidification of the vitreous humour filtrate, or in some cases by following the reduction in viscosity of hyaluronic acid due to disaggregation. Although a viscometric method is preferable, it could not be used here as increase in protein in the vitreous humour raised the viscosity and this overshadowed any possible fall due to change in hyaluronic acid.

The total nitrogen content of the vitreous and aqueous humours was determined to give a picture of protein movement in the eye and the hexosamine content was determined in the hope that it would reflect changes in the hyaluronic acid of the vitreous humour. The change in protein—which contains small amounts of hexosamine—was however so large that hexosamine change reflected only this.

In all these experiments one eye of each animal was injected with active enzyme and the other with an equal volume of the enzyme solution after inactivation by boiling.

METHODS

Total nitrogen was estimated by micro-Kjeldahl followed by distillation and titration, using the apparatus described by Markham (1942).

Hexosamine was estimated by the method of Elson and Morgan (1933) modified for use with small volumes. 0·5 ml. or less of vitreous humour filtrate or 0·1-0·2 ml. aqueous humour were used. The samples were put in small glass bulbs of about 3 ml. capacity and having a wide neck of about four inches long. The hydrolysis, acetylation and reaction with Ehrlich's reagent were all done in these bulbs without transfer and the final volume was brought to 3 ml. Colour was estimated by a Hilger Biochem absorptiometer, using Filter No. OG.1 (Hilger). A reagent blank and glucosamine standards were carried through all stages with each estimation.

State of aggregation of hyaluronic acid. The state of aggregation of hyaluronic acid was estimated by observing whether a fibrous or flocculent precipitate was given when the filtrate of the vitreous humour was added to acid acetone (Robertson, Ropes and Bauer, 1940; Pirie, 1949).

Preparation of hyaluronidase. The enzyme was prepared from rabbit testis by the method described by Madinaveitia (1941). The preparation was taken as far as the precipitation with NaCl and then dialysed against 0·9 per cent. NaCl. The dialysed solution was sterilised by filtration through a collodion membrane of a.p.d. 0·82μ.

Test of hyaluronidase activity. The disaggregating effect of the enzyme on the hyaluronic acid of the ox vitreous filtrate was used as a test of enzyme activity. Two ml. ox vitreous filtrate were mixed with 0·1 ml. enzyme at 30°. Samples were precipitated at intervals in 3 vol. acid acetone and the time taken for the enzyme to change the character of the precipitate from a compact fibrous one to a cloud-like precipitate was taken as an indication of the activity of the enzyme.

Method of injection of enzyme into vitreous humour. Dutch rabbits of either

sex and between four months and one year in age were used. The animals were anaesthetised with intravenous nembutal and the eyes were cocainised. The enzyme or boiled enzyme solution was injected a little behind the equator, care being taken to avoid the lens, which is large in the rabbit. A 26 gauge (American) needle on a 0·25 ml. syringe was used for injection. Enzyme solutions containing 0·15-0·25 mg. protein/ml. were used.

Preparation of aqueous humour and vitreous humour for analysis. In some experiments aqueous humour was removed from the animal during life. The animal was anaesthetised and aqueous humour removed by inserting a small glass capillary pipette through the cornea. About 0·2 ml. fluid ran into the pipette without suction.

At the end of the experiment the rabbit was killed either by a blow or with nembutal. The eyes were removed, carefully cleaned of all external tissue, rinsed in saline and then dried. The aqueous humour was then removed, the eyes dissected equatorially and the vitreous humour pulled away from the retina. The anterior half of the eye, together with the attached vitreous humour, was then put on a small glass mesh filter and allowed to drip into a centrifuge tube in the ice chest. Filtration usually took about ½-1 hour. The filtrate was then centrifuged to remove pigment and cells and the clear supernatant fluid analysed.

Results

Reaction of Vitreous Humour to Injection.—Injection of the active enzyme preparation caused a prolonged inflammatory reaction in the eye. This reaction also occurred after injection of the heated enzyme, or of saline, but was usually much less severe. I found that the reaction to the heated enzyme—a reaction that is presumably unspecific in nature, due to trauma or introduction of foreign protein—could be reduced if the volume of injected fluid were kept as small as possible. If 0·1 ml. of heated enzyme diluted 1/5 with saline were injected, the reaction of the eye was worse than to 0·02 ml. undiluted enzyme. Injection of 0·1 ml. into a rabbit's vitreous humour raises the tension to over 100 mm. Hg on the Maclean tonometer for a few minutes and it may be this sudden rise of tension that is responsible for the inflammatory response. The rise after 0·02 ml. injection is not noticeable.

Reaction to Active Enzyme.—Within two hours after injection, either of 0·02 ml. or 0·1 ml. enzyme preparation, the aqueous humour showed a marked flare. The fundus and vitreous humour appeared normal both to ophthalmoscopic and slit-lamp examination. After 24 hours the aqueous humour contained many circulating cells and a dense flare. The fundus was usually quite normal, but the central area of the vitreous humour was hazy. In three days the aqueous humour still showed a flare, but the number of cells was diminishing. The vitreous humour was usually full of brightly refractile particles, probably cells, sometimes attached in clumps to the back surface of the lens and scattered throughout the visible anterior part of the humour. The retina usually appeared normal, but in a few cases patches of

exudate appeared in the lower part of the fundus. From this time the anterior chamber gradually cleared and was usually normal in from six to fourteen days. The vitreous humour cleared more slowly and reached a steady state in about a month's time, when there would be a few cells visible. The normal rabbit's vitreous humour shows very little in the slit-lamp beam. The humours of the injected rabbits did not return to this optically empty state, but showed a few refracting streaks running usually vertically or at an angle of 45°. The vitreous humour did not appear grossly changed in any case.

Reaction to Heated Enzyme.—Injection of 0·02 ml. heated enzyme into the vitreous humour caused no reaction in the aqueous humour. Injection of 0·1 ml. enzyme diluted 1/5 caused in general a reaction similar to, but milder than, that caused by the active preparation. In two cases the reaction was indistinguishable from that to the active enzyme. The reaction in the vitreous humour was very like that to the active enzyme, both in type and in duration. In fact, it was noticeable that the difference between the two eyes, the one injected with active and the other with inactive enzyme, was more easily seen in the aqueous humour than in the vitreous humour, the site of the injections.

Effect of Hyaluronidase on Aggregation of Hyaluronic Acid.—The state of aggregation of hyaluronic acid was measured by the method described. Even with the small amounts of material available the change in type of precipitate after hyaluronidase action was perfectly clear. The normal vitreous humour, or the vitreous humour injected with heated enzyme, gave a very small fibrous precipitate in a clear supernatant. The vitreous humour injected with active hyaluronidase gave a cloud only, which might settle to a flocculent precipitate after some time. The activity of the enzyme used was such that 0·1 ml. of enzyme diluted 1/5 added to 2·0 ml. ox vitreous humour filtrate disaggregated the hyaluronic acid in it in 30 seconds at 30°.

Earlier experiments have shown (Pirie, 1949) that hyaluronidase acted much more quickly in the filtrate of the ox vitreous humour than in the intact excised eye and this was considered to be due to the restraining influence of the fibrous protein on the diffusion of the enzyme. One can, therefore, expect that an amount of enzyme which will disaggregate hyaluronic acid almost instantaneously in a vitreous humour filtrate may take some hours to act *in vivo*. The shortest time interval investigated was four hours and I found that after this time complete disaggregation had taken place in the living eye. Eyes removed at later intervals after injection showed that the hyaluronic acid of the vitreous

humour remained in the non-viscous disaggregated form for at least a month. Thereafter it seemed to return to normal. The humours that contained disaggregated hyaluronic acid were not liquefied, but were more fragile and filtered much more rapidly than the normal humours. The results showed quite clearly that rabbits killed up to six weeks after injection of hyaluronidase had disaggregated, and rabbits killed six or more weeks after injection had normal aggregated hyaluronic acid in their vitreous humours. In no case did injection of inactivated enzyme have any effect on the state of hyaluronic acid.

Changes in Nitrogen and Hexosamine after Hyaluronidase Injection.—Nitrogen and hexosamine were estimated in both vitreous and aqueous humours when the rabbit was killed. The time of death ranged from 4 hours to 8 months after enzyme injection.

There was a 2—3 fold rise in nitrogen, from 0·27—0·7 mg./ml. in the vitreous humour 24 hours after injection of active hyaluronidase. This was accompanied by a slight rise, from 40—100 μg./ml. in the hexosamine content. The vitreous humour injected with heated enzyme showed similar but slighter changes. Both nitrogen and hexosamine returned to normal about 28 days after injection of active or inactive enzyme.

The changes in the aqueous humour after injection of active enzyme into the vitreous were more pronounced and took place earlier than the changes in the vitreous humour which seems to show that there must be very rapid diffusion between the vitreous and the aqueous humour. Two hours after the injection into the vitreous humour, the aqueous humour nitrogen had risen 10 fold and remained between 3—6 mg./ml. for 24 hours. Hexosamine rose to 500—900 μg./ml. After 24 hours both nitrogen and hexosamine fell and were normal 14 days after the injection. The changes in the aqueous humour of the eye injected with heated enzyme were very much slighter.

The total nitrogen analyses showed that the influx of protein into the aqueous humour is much greater than into the vitreous. This is probably due to the fact that the increase in protein in the vitreous is due to a cell invasion, while soluble proteins derived from capillaries appear in the aqueous humour a short time after injection of active enzyme into the vitreous.

Discussion

The results reported briefly by von Sallmann (1948) showing that injection of hyaluronidase into the vitreous humour causes an inflammatory reaction, have been confirmed. The main point

of interest in the long-term experiments reported in this paper lies in the fact that some time after subsidence of inflammation the vitreous humour hyaluronic acid is again in the viscous, aggregated condition.

The return to normal of the vitreous humour hyaluronic acid probably shows that production of hyaluronic acid is a continuous process in the living eye. Liquefaction of the vitreous humour in man appears to be non-reversible, but judging by experiments with ox vitreous humour reported by Pirie, Schmidt and Waters (1948), liquefaction is more directly related to destruction of the fibrous protein of the humour than to change in hyaluronic acid. Meyer (1947) has already suggested that hyaluronic acid is constantly produced and removed from the eye. The experiments reported here give some proof for this by showing that in the living animal hyaluronic acid is gradually replaced in the viscous aggregated form after it has been hydrolysed by injected hyaluronidase.

The cells which produce hyaluronic acid either in the eye or elsewhere are not known. Hechter (1948) found that, in human skin, the effect of an injection of hyaluronidase on wheal formation (spreading factor effect) is lost after 24—48 hours, showing that in this tissue hyaluronic acid is either re-formed in this time, or diffuses in from surrounding areas. It seems unlikely that diffusion into the vitreous humour from surrounding tissues takes place and easier to consider that hyaluronic acid is re-formed in the eye.

If hyaluronic acid is formed in the tissues surrounding the vitreous humour and secreted in the aggregated form, its diffusion into the humour structure must be very slow. In the ox vitreous humour I found (Pirie, 1949) that hyaluronic acid washed out of the humour very slowly indeed and that it was always found in the disaggregated state in the wash water. The humour of the rabbit contains a lower concentration of hyaluronic acid than that of the ox and is less coherent and firm a structure, so that it is possible that hyaluronic acid diffuses more easily. On the other hand, it is possible that it is produced by the cells that invade the humour after enzyme injection.

Slit-lamp and ophthalmoscopic examination showed that no marked permanent change resulted from injection of hyaluronidase. It seemed possible that disaggregation of the viscous jelly of the vitreous humour might be reflected in changes in the intra-ocular pressure. Records of intra-ocular pressure were studied in five rabbits of the series, using a Maclean's tonometer. The tension of the eye injected with inactive hyaluronidase was also recorded, as the tension of the normal rabbit eye can vary

considerably. Injection of active hyaluronidase caused a reduction in tension to about half that of the eye injected with inactive hyaluronidase, within 24 hours of injection. Tension stayed at this level (10—11 mm. Hg) for three to four days, but was back to normal again nine days after the injection. One cannot say whether this reduction in tension is due directly to hydrolysis of the viscous hyaluronic acid of the vitreous humour, or to the resulting inflammation of the eye, but as little change in tension occurred in the control eye injected with inactive enzyme, it seems probable that some of the fall in tension was due to the change in state of hyaluronic acid in the vitreous humour.

SUMMARY

1. The hyaluronic acid in the vitreous humour is disaggregated by hyaluronidase injection and remains so for at least a month. After this time aggregated hyaluronic acid is found, showing that hyaluronic acid can be produced in or secreted into the vitreous humour during life.

2. Injection of rabbit testis hyaluronidase preparations into the vitreous humour of the rabbit caused a prolonged inflammatory reaction, noticeable within two hours in the aqueous humour and after 24 hours in the vitreous humour.

3. The nitrogen contents of both vitreous and aqueous humours are increased after hyaluronidase injection.

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BILATERAL CONGENITAL ANOPHTHALMOS*

BY

F. PAPOLCZY

BUDAPEST

ANOPHTHALMOS is one of the rarest of the developmental anomalies of the eye and it is usually bilateral. In the case described below an orbital cyst and other developmental anomalies were present.

Congenital anophthalmos was first described by Lyscostenes and later by Schenk (1609) and Barthelin (1657), but Briggs was the first to mention the hereditary character of this disease (Sorsby, 1934). At the beginning of the nineteenth century Briggs described a family in which, out of seven children of healthy parents, three were born with bilateral, and one with unilateral anophthalmos. Later Monteath (1821) and Walker (1831) emphasized the hereditary nature of the disease.

Manz (1876) says that in most cases of congenital anophthalmos rudiments of the eye can be found in the orbit. When this is not the case, however (Röder, Gradenig), the optic nerve is imperfect; it may be represented by strands of connective tissue, or it may be absent (Rudolphi). The foramen opticum may be constricted. Rudolphi claims that it is impossible to distinguish exactly between this picture and microphthalmos, and that anophthalmos is not a developmental defect of the eye, but atrophy due to some unknown injury in foetal life. He believes the pathogenesis of microphthalmos and anophthalmos to be the same.

Landesberg (1877) pointed out the importance of blood relationship between the parents. Hippel (1899) showed that cases of microphthalmos and of bilateral anophthalmos can occur in the same family.

Recent reports tend to confirm these earlier views. Cecchetto (1920), Ougaud (1922), Langon (1926) and Wirth (1938) all mention the parents as being related by blood. Hanke (1904), in a case of congenital bilateral anophthalmos could find rudiments of the eye, consisting of very small choroidal remnants embedded in fibrous connective tissue only by histologic examination after death. The infant had neither optic nerve nor tract on either side. Triepel (1920) reports that in his case there was atrophy of the optic nerve and chiasm. Gallemaerts (1924), in a case of bilateral anophthalmos found, after histologic examination, rudiments of the eye on the left side only; on the right side there were no traces of the eye.

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Neither side had optic nerve, or chiasm ; the corpora quadrigemina were defectively developed. Ougaud (1922) studied a family in which anophthalmos, choroidal coloboma and interstitial keratitis occurred. Canneyt and Vandemeulebroecke (1937) found unilateral and bilateral anophthalmos, microphthalmos and iris coloboma in four generations of one family. Wirth (1938) gave the history of three generations of a family with unilateral and bilateral anophthalmos, coloboma of the iris, the choroid and the crystalline lens, and congenital cataract.

In 1948, in this Journal, I presented the case of a ten-day-old boy with right-sided anophthalmos and orbital cyst, together with other developmental anomalies (proboscis on the right side, hare-lip and cleft palate). The rudiments of the eye were apparent only by histological examination of the contents of the orbit. Soon afterwards, the children's ward of our hospital, from which this patient had come, sent a six-months-old boy with congenital bilateral anophthalmos to the eye-department for examination.

FIG. 1.

FIG. 2.

1 He was the second child of a healthy mother of 22 years of age. The parents were not related. Wassermann reaction was negative. No developmental anomaly had ever occurred in the family.

Ophthalmological report:—Lids sunken on both sides, palpebral fissure shorter than normal (9 mm.), no eye on either side conjunctival sac very narrow. Rudiments of the eye neither visible, nor palpable. No other developmental anomalies. (Figs. 1 and 2).

X-ray examination:—The bony wall of the orbit, as well as the optic canals much narrower than usual on both sides. In profile the forehead appeared flattened, the cranial basis shortened, the three cranial *scalae* situated on one level. The sella smaller than normal, but clearly defined. Encephalography revealed no essential anomaly.

The child being alive and well, there was neither *post-mortem* nor histological examination.

According to the literature, in cases of congenital anophthalmos there is generally a record of blood relationship between the parents or a family history of anophthalmos or other developmental anomalies. It may happen, however, as in the cases of Hasner (1876), Wicherkiewicz (1899), Hanke (1904), Triepel (1920), Ventola and

Zembrano (1946) that neither were the parents related, nor—which is more important—did the condition appear to be hereditary or associated with other developmental anomalies. This is not inconsistent with the hereditary character of the disease. It may be that the parents cannot give exact information about their family history; moreover, the child afflicted with anophthalmos may become the founder of a family suffering from this or some other developmental anomaly.

By clinical examination I could not detect rudiments of the eye on either side. But it has been shown in the literature that when the child dies and *post-mortem* or histological examination can take place, rudiments of the eye are usually found in the soft parts of the orbit. From the X-ray examination we may deduce that the optic nerves or perhaps the chiasm and tracts were defectively developed but positive radiological proof of this is lacking.

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A THERAPEUTIC STEP IN CHRONIC GLAUCOMA*

BY

G. DE L. FENWICK

A MEASURE that is sometimes very useful in treating an attack of acute glaucoma is the retrobulbar injection of novocain (procain), administered not pre-operatively, but as an isolated therapeutic incident (S. Gifford, M. J. Icaza). It does not of course have a permanent effect. so that an operation becomes necessary sooner or later; but the object of the injection is to avoid the performance of

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a Graefe iridectomy on a haemorrhagic painful eye, in a sick exhausted patient; for the results of these operations, whether done with local or general anaesthesia, are inferior to those of the "quiet" glaucoma operations, leisurely performed. Retrobulbur injections have certain risks, of which the chief is retrobulbar haemorrhage, but it is believed that this danger can be eliminated by the use of a specially designed needle. These matters will be discussed later in this paper.

The following histories demonstrate the possibility of success with this treatment; others could be quoted in which it was entirely without effect; why it succeeded in some cases and not in others is not known. Accurate statistics are not yet available, but it appears that the injection will produce the desired result in about one quarter of the cases in which it is tried; the desired result being the establishment not necessarily of normal tension, but of a comfortable white eye which can be trephined in due course.

CASE HISTORIES

1. I., female, aged 64 years, came to Moorfields August 5, 1947, with pain in R. eye of 2 weeks duration; typical acute glaucoma, VA=4/60; treated with 1 per cent. oily eserine and heat every 15 minutes, but after several hours of this there was no improvement whatever. Was then given a retrobulbar injection of 1 c.c. of 4 per cent. novocaine containing 0·1 c.c. of 1/1000 adrenalin and eserine was resumed; his pupil soon contracted, his pain subsided and his tension fell, though it was not normal until next day. The eye was trephined in March, 1948, with a satisfactory result.

2. J.G., male, aged 60 years, attended January 6, 1949, with a pain in R. eye which had lasted 8 days; congestion, corneal oedema, shallow A.C.; tension (digital)="+" (35 to 50 Schiötz); VA=counting fingers; L. eye blind; was treated with eserine and heat, as in Case 1, but without any improvement, was then given a retrobulbar injection as above, which reduced the tension to normal in an hour. Eserine was continued, but *next day the tension began to rise again. On the third* day the injection was repeated (this time without adrenalin), the tension again fell to normal, the eye whitened and was trephined an hour later; VA=6/6.

3. A.P., aged 56 years. Onset of acute glaucoma in L. eye October 22, 1948; intensive eserine and heat treatment instituted the same day but without effect; next day was taken to theatre and given 1·5 grm. sodium pentothal intravenously, as this anaesthetic, when previously used for glaucoma iridectomy, had been observed to reduce the tension; it fell very slightly and then became stable; half-an-hour later, retrobulbar novocaine and adrenalin were given and considerable improvement was almost immediately evident in cornea, pupil and tension. He returned to bed and the improvement was maintained. November 2, L. trephine, December 11, VA=6/9.

DISCUSSION OF CASES

In Case 2 the tension fell after the first injection, only to rise later, presumably because of absorption of the novocaine. A second injection reduced it again, and the operation was performed without delay lest it should rise a third time. Perhaps in this case, after the first injection had reduced it, it could have been kept down by the use of miotics other than eserine; for Scheie and Ojers believe

that retrobulbar novocaine, by paralysing the ciliary ganglion, inhibits the formation of acetyl-choline in the pupillary nerve-endings, and so renders eserine (but not pilocarpine) ineffective. However, in the present writer's brief experience, eserine has been observed to maintain pupillary constriction after cataract extraction, even though a complete extra-ocular paralysis had been pre-operatively induced.

In Case 3, one cannot say with certainty how much the fall in tension was attributable to the retrobulbar injection and how much to the pentothal, but it seemed to be largely due to the former.

Dangers of Retrobulbar Injections

1. The chief danger is *retrobulbar haemorrhage.* See below.

2. *Transient blindness.* This has been described by Ida Mann, occurring in an otherwise healthy woman aged 35 years, after retrobulbar novocaine-adrenalin for repair of a retinal detachment. A few weeks later the same injection was given (for a second operation), but this time without harmful effect; the operation was successful, the visual acuity being 6/6. The temporary blindness was thought to be caused by the needle-tip piercing the sheath of the optic nerve and allowing the solution to infiltrate its fibres. Bidault saw a similar occurrence in a patient with senile macular lesions. He attributed it to constriction either of the central retinal artery or of other vessels entering the optic nerve from the opththalmic artery.

3. The injection is usually said to cause pupillary dilation. This would be a disadvantage in glaucoma, but appears to be only a theoretical one.

4. The optic nerve might be damaged in clumsy hands.

5. Orbital infection. This is, or should be, unthinkable.

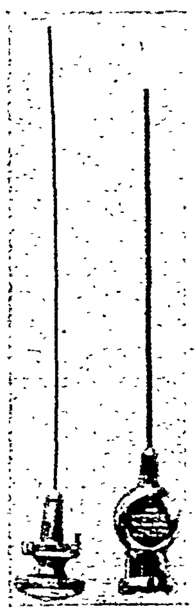
Retrobulbar Haemorrhage

In the Moorfields theatres some six haemorrhages are seen every year—*i.e.*, one haemorrhage in about 160 injections. The majority of these injections are given for cataract or detachment operations, but even for these non-urgent procedures a haemorrhage (and the necessity to defer the operation) may have unsatisfactory results; as in the case of a nervous patient who after such a postponement, could never be persuaded to enter the theatre again. If the postponed operation is urgent, as in acute glaucoma, the situation can be more serious; two cases are known to the writer: in the first, the haemorrhage necessitated a postponement of an urgent glaucoma iridectomy for five days; as a result, this patient left hospital with extremely poor vision. In the second, likewise, iridectomy had to be deferred, but happily the glaucomatous attack subsided and the

patient went home with an efficient (though black) eye; such good fortune would be exceptional.

Traquair believed that haemorrhages could always be avoided by slow careful injection, and many surgeons hold the view that if the solution is being constantly forced out of the advancing needle, it is impossible to enter a vessel. However, haemorrhages have occurred even when these criteria were fulfilled. One would expect them to occur more often if the needle point is passed to the very apex of the orbit (as recommended by H. Gifford), for here the vessels are larger and more fixed; one would also expect them more often in inflammatory conditions because of orbital congestion. Goulden considered that the incidence could be reduced by using a needle with a slightly blunt point.

To reduce the risk of haemorrhages, a blunt needle with a sharp stylet has been designed.



Length of needle	... ...	50 mm.
External diameter	... ...	0·7 mm.
Base ...	ordinary Record syringe fitting.	

Technique of Retrobulbar Injection

The needle with the stylet in it is passed through the skin in the usual inferotemporal position just inside the orbital margin. This takes more pressure than with an ordinary retrobulbar needle because of the shoulder and the greater diameter; in a hypersensitive patient, therefore, a few minims of novocaine could be injected into the skin first; but this is not usually necessary if the stylet is really

sharp. The needle and stylet are now advanced until one feels the orbital septum being pierced. As soon as this is passed, the stylet is withdrawn, and the blunt-ended needle can now be moved on safely. Often the needle-tip is felt meeting another fascial layer—the sheet that extends between the lateral and inferior recti. If pain is experienced here one can fit the syringe to the needle and inject 0.5 c.c. of novocaine before proceeding. After this sheet has been passed, the end of the needle lies within the muscle cone (the ideal position for it is 2 mm. below and behind the posterior pole of the eye) the ciliary ganglion lies some 7 mm. behind the posterior pole, so if the needle-tip is in this situation, the solution flows into this 7 mm. space and infiltrates the ciliary nerves and ganglion. 1.5 c.c. of 4 per cent. novocain are used. It usually contains 1/1000 adrenalin, 1 minim to the c.c., but in case 2 described above the second injection was successful without adrenalin. It seems doubtful whether adrenalin is essential to its success, and occasionally it has produced alarming anginal reactions. It is not suggested that this needle should be used for every retrobulbar injection, but only where it is particularly important to avoid a baemorrhage.

Rationale

We do not know how retrobulbar novocaine relieves an attack of acute glaucoma. Its effect could be due to:

(*a*) Extra-ocular muscle paralysis. The fall in tension that occurs after ordinary pre-operative retrobulbar injections (as for cataract extractions) is attributed to this, but it cannot be important in acute glaucoma.

(*b*) Inhibition of parasympathetic activity. This explanation is not easily supported anatomically; for the only para-sympathetic fibres that are known to pass to the eye are those that terminate in the sphincter pupillae and ciliary muscle, and inhibition of these would be expected to aggravate narrow-angle glaucoma, not relieve it. There is no evidence that any vasodilatator fibres supply the eye (Duke-Elder).

(*c*) Inhibition of sympathetic activity. Thiel found that the tension in glaucomatous eyes was reduced by ergotamine. This drug, though vasoconstrictive, is in general antagonistic to adrenalin and sympathetic activity, and he concluded that glaucoma may be due to an increase in sympathetic tonus. If this were so, the success of retrobulbar injections would be a fairly logical consequence.

(*d*) Interruption of Reflexes. It seems possible that the injection reduces the tension by breaking two reflex arcs. One of these is a conscious cycle—the increasing pain of acute glaucoma induces a mental state which aggravates the tension. The other one is autonomic, but its exact pathways are not known (*b* or *c*, above). Probably an important part in the aetiology of acute glaucoma is played by axon reflexes (*i.e.*, local reactions in the eye, liberating histamine); but these reflexes occur whether the main sensory trunks are intact or not, so they do not explain the beneficial effect of the injection. However, the mechanism may be similar to that of causalgia. In this disorder there is, in the affected limb, pain and

congestion which may be relieved by the injection of anaesthetic solutions into the trunk of the sensory nerve concerned. Lewis suggests that the symptoms of causalgia are due to release of histamine-like substances in the skin as a result of abnormal impulses passing in a centrifugal direction along the affected sensory nerve.

Conclusion

It is suggested that a retrobulbar injection of novocaine should be tried in all cases of acute glaucoma which are not improving after 24 hours of the usual intensive treatment—miotics, counter-irritants and sedatives. The chief danger of this measure, *viz.*, retrobulbar haemorrhage, has, it is hoped, been eliminated by using a needle on the trocar-and-cannula principle.

Summary

1. Some cases of acute glaucoma can be terminated by a retrobulbar injection of novocaine; three such are described.
2. The risk of an orbital haemorrhage is important.
3. This can be avoided by using a special needle.
4. The rationale of the procedure is discussed.

Acknowledgment

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EARLY POST-OPERATIVE DETACHMENT OF THE CHOROID*

BY

FRANCIS CSILLAG

BUDAPEST

EARLY post-operative detachment is a secondary and long known phenomenon. It occurs as an unexpected sequence after cataract glaucoma, iridectomy, trephine, sclerectomy and cyclodialysis operations. Its incidence, according to the various authors, varies much The highest percentage is reported by O'Brien, who states that 62 per cent. of his operations were immediately followed by detachment of the choroid.

Origin of the detachment is explained differently by various authors. Fuchs assumes a warping of the choroid, while Meller and O'Brien believe an imperfect healing of the incision to be responsible. Meesmann, Hagen, Urbanek and Fronimopoulos think the post-operative hypotony to be of significance. Lindner is of the opinion that the contracting vitreous body exerts traction on the choroid. Bonnet and Grandclement assume a relationship with existing general or ophthalmological disease. A considerable number of the authors think that behind the detached choroid, blood (Urbanek) or fluid accumulates, but they differ concerning the origin and the active or passive consequences of the same. A transudate from the choroidal vessels is assumed by Hagen, O'Brien, Fronimopoulos and Meesmann, whereas Meller thinks that the ciliary body forms the liquid. H. D. Mayer (1939) states that the aqueous oozing backwards through the loosened attachment of the ciliary body forces the choroid off its base. The cause of hypotony is the increased outflow of the aqueous. If the anterior chamber is well preserved and pressure remains normal, she believes serous exudation to be of importance.

Csillag has emphasized in his lecture (delivered at the Hungarian Ophthalmological Society, 1939), *that if during operation a communication* is established between the anterior chamber and the supra-choroidal space, the aqueous oozes backwards and detaches the choroid. The increased outflow of the aqueous causes a shallow chamber to form and hypotony to ensue. His lecture has been published late, owing to war-time difficulties.

The choroid adheres to its base only at the head of the optic nerve and where the veins perforate the sclera. The operative deformation of the eye-ball may cause the choroid to become loose and warp at its base (commotio of the choroid). The decrease of

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pressure may permit transudate from the vessels to enter the supra-choroidal space, gently elevating the choroid (amotio of the choroid). Such a detachment is small and flat, and the fluid behind it is of insignificant amount (O'Brien's frequent detachments seem to have been of this kind). Such detachments should not be regarded as being genuine ones (ablations), as, following reunion of the lips of the incision and re-establishment of intra-ocular pressure, they tend to disappear.

Three different methods of cataract extraction were used at the ophthalmic clinic of Budapest University at a certain time. The origin of the choroidal detachment depended, as the author was able to ascertain, chiefly on the method of incision and partly on that of extraction. The least number of detachments followed incision which was conducted entirely within the limbus (conjunctival apron); they became more frequent following the conjunctival flap method (the incision can be finished sclerally in that case), and the most frequent detachments occurred, despite correct operation and uneventful healing, following Horváth's scleral flap method. Intracapsular extraction and subsequent extraction of the capsule increased the incidence of detachment.

This incidence is demonstrated by the following table:

Method of incision	Intracapsular extract.	Intracapsular detachm.	Intracapsular detachm. per cent.	Extracapsular extract.	Extracapsular detachm.	Extracapsular detachm. per cent	Total extract.	Total detachm.	Total detachm. per cent.
Conjunctival apron	279	2	0.72	136	1	0.73	415	3	0.70
Conjunctival flap	79	2	2.53	74	1	1.35	153	3	1.96
Scleral flap ...	334	14	4.19	193	4	2.07	527	18	3.41
Total	692	18	2.60	403	6	1.48	1095	24	2.19

Only those cases were investigated for detachment which were conspicuously late in re-filling the chamber. Thus only those cases remained undetected, which required 2 to 3 days in re-establishing the chamber and the detached part was replaced on the 6th to 7th day at a time, when it became possible to examine the eye with a mirror. Therefore we may assume this post-operative complication to be more frequent than is shown in the table above. But all sorts of incision may react likewise and therefore the relative probability and conclusions drawn therefrom remain the same.

Detachment more frequently occurs after complete iridectomy and following basal iridectomy, but there is no considerable difference. Various iris operations have not been included in the table, not being of decisive influence concerning detachment. The extraction has been regarded as being intracapsular when the lens was removed

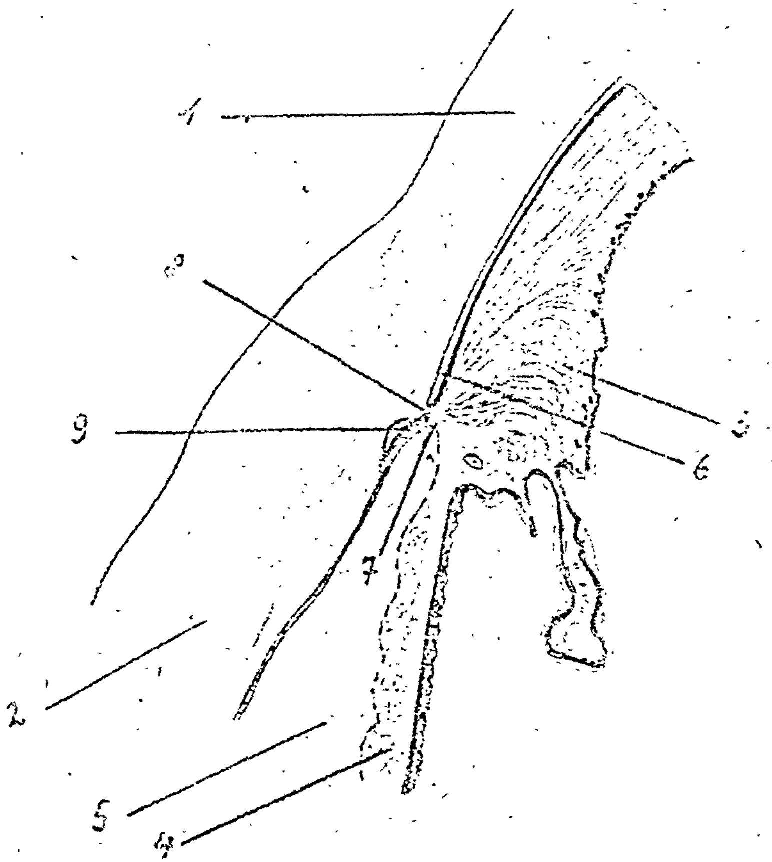
together with an intact capsule. I believe it is unlikely that detachment is influenced by age, sex, ocular alteration or systemic disease.

After cataract extraction the intra-ocular pressure decreases, the vessels of the choroid dilate and gently push the vitreous body forward. As soon as the wound closes, the accumulated aqueous refills the vitreous body and the deep chamber, which characterizes aphakia. The physiological equilibrium between loss and production of aqueous re-establishes itself, and intra-ocular pressure stabilizes. The patients were not examined by a retinoscope on the days immediately following operation. Perhaps this circumstance accounts for the fact that detachments were less frequently noted by us than by other authors, and none of the aforesaid flat detachments called "amotio" occurred. The onset of detachment is shown by the chamber remaining flat for days, and by hypotony. The detachments began in the upper half (or were drawn up there), and proceeded from there downward and backward. Even simple illumination discloses the dark-grey object bulging into the vitreous body, situated next to the ciliary body, which can be trans-illuminated through the sclera.

A conspicuous feature in our cases was a shallow chamber, despite a perfectly closed wound. So a shallow chamber does not necessarily mean faulty healing. Therefore defective filling of the anterior chamber in the case of a well-closed wound, should be ascribed to something else. Our attention was particularly called to the fact, that in cases where the re-establishment of the chamber, due to an imperfect reunion of the lips of the incision, was retarded, though the eye remained soft, the choroid remained in its proper place. With one of our cases, two weeks after intra-capsular extraction, the chamber remained so shallow on account of the filtrating wound, that the bulging membrane of the vitreous body touched the cornea. Two months after operation the chamber was still flat, and ocular pressure was 15 mm. Hg. Nevertheless, the choroid remained *in situ*. Consequently the detachment cannot be ascribed to a leaking wound and subsequent hypotony, because then it should be present in every such case, and again a mal-united wound should characterize every detachment. Actual observation confirms the opposite: detachment is less probable, if the wound leaks outwardly. Nevertheless I do not believe that an outward filtrating wound necessarily excludes detachment.

As the table shows, most detachments occurred following the scleral flap incision. Since this operation differs from the others only by the form of the incision, the cause of detachment has to be sought for in this direction. Before incision within the limbus is finished, by means of Graefe's knife a 3 mm. long and broad flap is cut out upwards through the half thickness of the sclera, as has been described already by Horváth (1939), the originator of this method.

The anterior chamber is separated from the supra-choroidal space only by the trabecular tissue of the angle of the former, and the anterior end of the ciliary muscle attached to the corner of the chamber (see Fig.). The thickness of this part, its distance from



1 The sclera; 2 cornea; 3 ciliary body; 4 iris; 5 anterior chamber; 6 supra-choroidal space; 7-9 anterior end of the ciliary muscle, scleral spur and trabecular tissue of the angle of the anterior chamber (line of cleavage).

the limbus, and the thickness and curvature of the sclera vary in individuals, although only by small differences. On account of this it is rather difficult to cut a 3 mm. flap off in such a manner that it should not contain the entire thickness of the sclera in the form of a central strip. By slicing the sclera, the separating part is easily cut, whereby a small cleft is formed between the anterior chamber and the supra-choroidal space so that both communicate.

As soon as the wound closes, the accumulating aqueous does not press the slightly bulging vitreous body back, and does not form the anterior chamber, but finding less resistance along the communicating intra-ocular way, leaks backward behind the choroid and lifts the latter from its base. The chamber, despite a well-joined incision, remains therefore shallow as long as the aqueous leaks backward. As soon as the incision closes, normalisation of intra-ocular pressure begins but is not completed so long as the continually produced aqueous is absorbed through the choroid, as well as by the physiological way. This explains the high-grade hypotony accompanying detachment. The anterior chamber fills up and the intra-ocular pressure rises as backward leakage decreases. As soon as lateral seepage becomes less than absorption, detachment decreases accordingly. As the aforesaid communication closes, the aqueous is progressively absorbed beneath the choroid, the choroid sinks back again, and the intra-ocular pressure is re-established.

In five of our cases the anterior chamber was re-established after operation, but emptied after a few days, despite perfect outward closure of the incision. This delayed intra-ocular abortion of the chamber may have been due to the part separating the two cavities having been only damaged by the incision, and not cut entirely; a certain pressure of the aqueous collecting after the wound being closed, is obviously necessary for penetration.

Detachment after intra-capsular extraction is much more frequent, if the attachment of the ciliary body is disturbed by the incision (scleral and conjunctival flap). The traction of the zonular arch may complete the still imperfect communication. This rôle of the zonular arch becomes the more obvious, the more the incision is scleral (see table). Probably a forced traction of the strong zonular arch, together with a simultaneous loosening of attachment of the ciliary body, suffices to cause detachment. Loss of vitreous may sponsor detachment.

Accepting the aforesaid views, we may understand why, in the case of a badly united incision, despite the shallow chamber, no detachment occurs. An imperfectly closed wound does not promote, but rather inhibits detachment, because in the meantime, owing to aqueous loss, the angle of the chamber may close. In one case the detachment occurred 6 days after operation, despite the anterior chamber remaining shallow the whole time on account of an imperfectly united incision. Aqueous seeped without difficulty outwards, and leaked more thoroughly beneath the choroid only after the incision had closed. The choroidal vessels may rupture during operation if the patient's blood-pressure is high. The ensuing haemorrhage may detach the choroid. There were no signs of inflammation associated with the choroidal detachment and no

evidence of any general medical disorder. The intra-ocular pressure before operation was normal. On the basis of these phenomena the author succeeded in inducing choroidal detachment experimentally in animals.

Prognosis of early post-operative detachment is good. The time of complete replacement of the choroid depends on the time elapsing since the complete closure of the angle and on the degree of detachment. It usually takes 1 to 2 weeks. Most authors agree that, if the replacement of the detachment is perfect, no serious consequences follow. I believe that hypotony following operation may even be advantageous for healing of the incision. Prognosis of detachment due to haemorrhage is less favourable. Verhoeff, Filatov, Averbach, and Vail succeeded in saving some sight by instantaneous scleral puncture following an expulsive haemorrhage.

Views on treatment vary. Müller recommends puncture to avoid functional disturbance. Elschnig also stated that a rapid cure followed puncture of choroidal detachment cases which had persisted for weeks after operation, but he recommended it only if the detachment was not due to haemorrhage, and the peripheral circulatory system was in perfect condition. Löhlein proposed cauterisation of fistula-forming wounds. Axenfeld proposed compresses. Imre was satisfied by the effect of pilocarpine. He believed that it caused hyperaemia and swelling of the ciliary body, which helped in the closure of the angle of the chamber.

I believe that detachment following glaucoma iridectomy originates in the same way as that following cataract operations. In our cases following trephine and cyclodialysis detachment also occurred repeatedly. In my experience, anti-glaucoma operations accompanied by detachment were always successful, the eye becoming hypotonic. In case of tissues becoming opaque by operative haemorrhage or pressure following glaucoma operation, examination for detachment is inhibited; furthermore, it is hindered by the narrowness of the pupil, or peripheral position of the detachments. The opening of the filtration angle by cyclo-dialysis is violent and blunt, and any ensuing haemorrhage may soon obstruct the path of the aqueous. This circumstance may account for the comparative rarity of detachment following this operation.

Imre sometimes used scleral puncture by electro-cautery for glaucoma, and this was sometimes followed by choroid detachment. The cauterisation of the sclera softens the eye, and choroidal detachment is a post-operative complication. Closure of the wound increases the intra-ocular pressure. In this case no backward seepage of the aqueous can be assumed, as the operation is remote from the filtration angle. Detachment in such cases is of different origin. It is not only promoted by decrease of intra-ocular pressure,

seepage of the vitreous body, and its shrinkage, but the haemorrhage and transudate elicited by thermic effect elevate the choroid. In choroidal detachment caused by backward seepage of aqueous, as described above in connection with cataract and glaucoma operation, hypotony stops only after the choroid is replaced, whereas in the case of ignipuncture the intra-ocular pressure increases, despite the persistance of the detachment, even after the wound has closed.

Summary

The onset of choroidal detachment following cataract extraction is influenced by the type of incision, the method of traction and by the auxiliary manipulation applied. If during operation the supra-choroidal space is opened by the incision, a communication between the anterior chamber and the former is established. The aqueous oozes backward beneath the choroid, and raises it from its base. Therefore the chamber is shallow, despite the incision being closed towards the palpebral aperture. Hypotony of the detached eye is due to the constant absorption of the aqueous. As soon as the filtration angle is closed, the backward leakage of the aqueous stops, the chamber is re-established, the intra-ocular pressure becomes normal; the fluid from beneath the choroid becomes absorbed, slowly the choroid becomes replaced and no further damage is done. Similarly are explained detachment following anti-glaucomatous operations.

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PRIMARY TUMOUR OF THE OPTIC NERVE*
(Glioblastoma Multiforme)

BY

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PRIMARY tumours of the optic nerve are rare. Nordmann states that Hidan estimates their frequency at 1 :25,000 patients, Bennett at 1 :35,000 and Lundberg at 1 :68,000. Duke-Elder (1940) refers to information from Moorfields (Collins and Marshall, 1900) from which it appears that only two such cases were found among 388,000 patients, and that approximately 350 had been reported in the entire literature. Nordmann further states that Morax (1926) found only three cases of tumours of the optic nerve among 61 neoplasms of the orbit. In 1930 Mathewson pointed out that 80 per cent. of optic nerve tumours were gliomatous, and originated from the nerve itself, while the rest originated from the nerve-sheaths.

The first complete description of such a tumour was given by v. Graefe (1864), but much work has been done since that time in order to clarify the clinical picture of this condition, especially as regards the pathological findings and the terminology. The following quotations from Duke-Elder, however, suggest that considerable confusion still exists: "The nature of the neoplasms, however, remained controversial and in the earlier literature an amazing confusion of terminology is encountered: glioma, gliosarcoma, fibroma, fibrosarcoma, myxoma, myxosarcoma, sarcoma, neuroma, endothelioma, fibromatosis, and so on. They were variously considered mesoblastic or epiblastic, benign or malignant, a hypertrophy or a neoplasm, the pathological diagnosis being changed from time to time and different views being expressed as to their significance and prognosis." It therefore seems justifiable to report a case of optic nerve tumour and to discuss the problems of exact diagnosis.

Case Report. E.G., a 43 year-old woman, was admitted to the Eye Clinic with the diagnosis of orbital tumour. During the preceding four months the patient had noted a marked decrease in vision of the left eye, and simultaneous protrusion of the eye-ball. There was no history of pain or diplopia other than headache, and she stated that she had been perfectly well and able to do full-time work.

Physical examination, August 22, 1941. The patient appeared to be in good general condition. Local examination revealed the left eye protruding more than the right. Exophthalmometer readings were 21 mm. in the left eye and 18 mm.

* Received for publication, March 16, 1949.

in the right. The left eye could not be pressed into normal position. The mobility of the eyes seemed to be normal. No tumour could be palpated in the orbit. There was no evidence of metastasis to regional lymph nodes, nor any pulsation or *bruit.* The left eye was normal as to the cornea, anterior chamber and iris. The pupil reacted indirectly to light. Ophthalmoscopy demonstrated a mushroom-like disc, protruding approximately 9 dioptres. The retinal vessels were enlarged and tortuous, and there were several retinal hemorrhages.

The right eye was normal. Visual acuity: R. 5/5; L. amaurotic. Visual fields: Normal. Intra-ocular pressure: R. 24; L. 14 mm. Hg. Laboratory tests: Urinalysis negative. Serology (Wassermann) negative. Roentgenogram demonstrated a normal skull, left orbit and optic foramen. A week later another roentgenogram revealed a slight widening of the left optic foramen. On September 10, 1941 the patient was dismissed without treatment, but she was ordered to return at regular intervals. Approximately five months later the patient was admitted to the clinic for an examination as the left eye had become red and painful. *Physical examination January* 23, 1942: The protrusion of the left eye was unaltered, but the mobility was somewhat reduced.

L. eye: There was ciliary congestion with the beginning of a *caput medusae.* The cornea was clear. The iris was hyperaemic and showed small haemorrhages Ophthalmoscopically there were no significant changes from August 22, 1941. R. eye: Normal findings. Vision 5/5. Visual field normal. The intra-ocular pressure now was 24 R., and 33 mm. Hg. L. Roentgenogram was taken on January 1, 1942, with the report that since August 8, 1941, a definite widening of the left optic foramen had appeared, and that the outlines of the foramen were blurred.

Summary of examination:

(1) Proptosis of the left eye straight forward and irreducible.
(2) Complete failure of vision had developed simultaneously with the protrusion.
(3) Papilloedema with haemorrhages.
(4) No history of diplopia. Mobility was at first normal, but decreased slightly.
(5) Pain in the eye occurred in association with increased ocular tension.
(6) Widening of the optic foramen over a period of approximately five months.

The patient had been in good health, and there was no evidence of any other diseases.

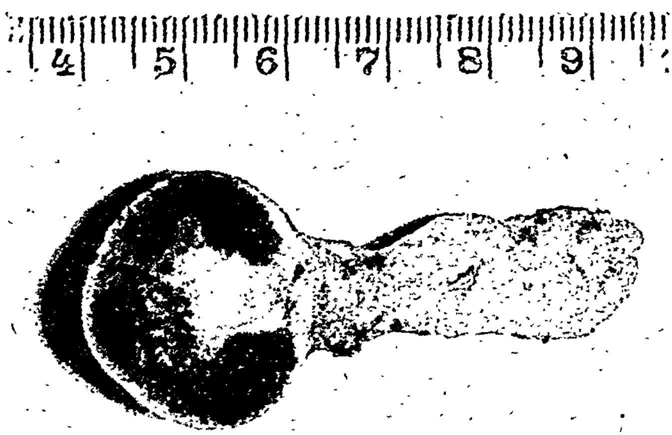

FIG. 1.

The enucleated eye with fasciculus opticus, which has circular constrictions and spool-like swellings.

These findings indicated a tumour of the left optic nerve.

As the eye was afflicted with increased intra-ocular pressure, blindness and pain, we decided to excise it together with the suspected tumour. During the operation one could feel enlargement of the optic nerve with scissors, and by drawing the eyeball forward as much as possible, one had the impression of cutting the nerve behind the tumour. A subsequent pathological examination demonstrated that removal of the tumour had been incomplete. The patient was told this, and

FIG. 2.

Expansively growing tumour limited to fasciculus opticus, which is surrounded by leptomeninges (x) and dura (D). Septa (St) with abundance of connective-tissue and blood-vessels give the tumour tissue a lobular appearance with some dense areas of small cells (s-s). Paraffin preparation. Hematoxylin-eosin staining. Magnified ×73.

that an intra-cranial operation would be necessary. She opposed this proposal, and was then dismissed from the clinic one month after the operation, during which time she received X-ray treatment. She was also advised to continue with X-ray therapy in her home town.

The patient subsequently returned twice for control during the first six months. She had felt well, and, was working at her farm. The other eye was normal, and there were no signs of intra-cranial complications. She now failed to return for her appointment, and her physician reported that the patient died one year after the operation, with increasing cerebral symptoms. No autopsy was performed.

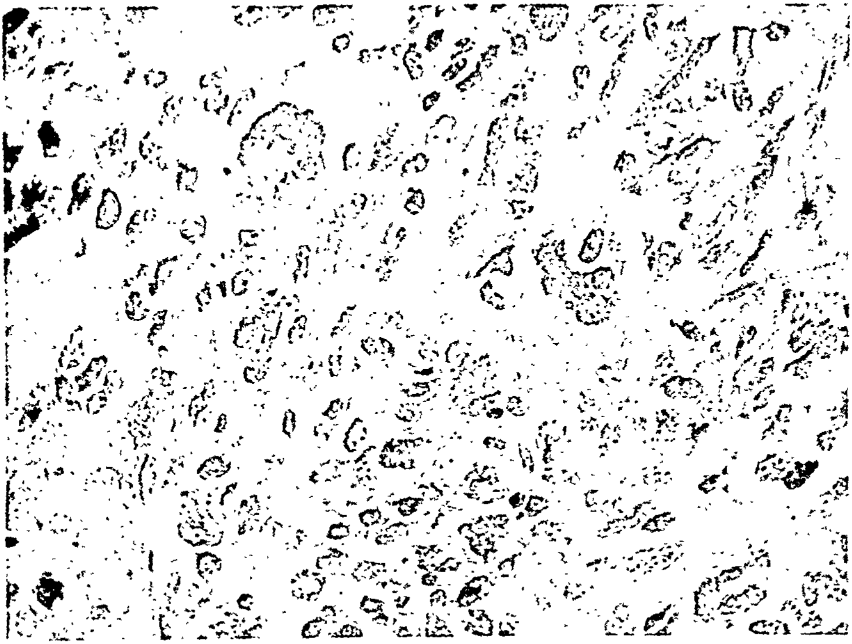

FIG. 4.

Slide demonstrating the variation in size, shape and staining reaction of cells and their nuclei. Note also the tumour's giant-cells. Paraffin preparation. Stained with hematoxylin-eosin. Magnified ×400.

cells show no definite orientation, giving off their processes in all directions, although these are often closely related to the perivascular membranes. Some of the nuclei are very large. Mitoses are frequent, and occasionally incomplete. Multinucleated forms are also present.

In one area of the cross-section of the cerebral portion of the nerve the tumour tissue is looser and infiltrated with a number of glial fibres. Palisade formations of pyknotic nuclei surround small, oblong, circular and triangular areas of necrosis. Besides these distinctly degenerated areas one can see throughout the whole tumour tissue small areas of various size in which the cells are not degenerated but show definite pyknotic nuclei.

There are mild reactive changes in the vessels in some places, with increase in the number of endothelial nuclei.

No nerve fibres were found in the paraffin sections examined, nor were there any melanin-pigmented cells.

Conclusion : In the pathological examination of the thickened fasciculus opticus an expansively growing and polymorphic tumour is found, with numerous primitive cell-forms of gliomatous types, continuing to the edge of the resection. Diagnosis: Glioblastoma multiforme.

Discussion : As no symptoms or signs were found indicating

that the tumour might be a metatasis from other organs, it was presumed to be primary. As mentioned above, uncertainty exists as to the classification of the optic nerve tumours. Hence it has been particularly difficult to decide upon the origin of the various neoplasms, e.g., whether they were intraneural (ectodermal) or whether they originated from the inner nerve-sheaths (mesodermal). Rönne (1931) holds that this confusion originates from the fact that in a great number of cases the nerve and its inner sheath are both affected.

Hudson (1912) divided these tumours into three types: I, Gliomatous; II, Endothelioid and III, Fibromatoid, of which the first originated from the nerve itself, and the last two from the sheaths.

Duke-Elder (1940) gives the following classification: I, Essential (Ectodermal) tumours of the nerve—Gliomata; II, Meningiomata, mesodermal tumours of the sheaths. (*a*) Endotheliomata and (*b*) Fibromata; III, Neuro-ectodermal tumours. (*a*) neurinomata and (*b*) malignant melanomata.

Although doubt may exist as to the exact pathological diagnosis in the present case, it most likely belongs to group I, gliomata. The microscopic picture is, however, characterized by considerable polymorphism, and therefore the diagnosis glioblastoma multiforme is made. It also appears that the leptomeninges were infiltrated by lymphocytes and fibroblasts, while the dural sheath was free. Likewise the eyeball itself was not infiltrated, but the tumour spread backward to the brain. In contrast to gliomata, the endotheliomata usually show a marked tendency to infiltrate the dural sheath and hence grow into the orbit. There are, however, some peculiarities in the clinical course of this case. In the literature it is stressed that the gliomata are of such slow development that they may even be considered benign. In the present case the progress of the tumour was rapid, and death occurred approximately two years after the onset of symptoms. In harmony with this view is the widening of the optic foramen on repeated roentgen examinations during five months.

The disease appeared in the present case at a relatively late age, 43 years. Other authors have shown that gliomata of the optic nerve usually start at an earlier age. Hence, Hudson (1912) found that 75 per cent. of the cases occurred in the first decade, and in 88 per cent. before the age of 20. The same author mentions also that endotheliomatous tumours, in contrast to the gliomatous, usually appear later, with an average of 35 years.

The other signs were as expected in this type of optic nerve tumour. Exophthalmos was present in a moderate degree. The

proptosis was straight forward, which is typical of optic nerve tumours and an important sign in the differential diagnosis from other orbital growths. Failure of vision, which in the present case occurred simultaneously with the proptosis, progressed rapidly to blindness. This is a usual feature in these tumours, and Braunschweig (1895) demonstrated that 33 of 44 cases with optic nerve tumours were amaurotic. Reduction of vision in such cases may also be due to secondary changes, e.g., papilloedema and haemorrhages. As the affected eye was blind at the first examination, no defect in the visual field was found. At an earlier stage such may be found, and by spread of the disease to the chiasma, such a defect may even be found in the other eye.

Diplopia is rare in this condition, and this accords with the fact that mobility of the eye may long remain unimpaired. By the time mobility is retarded, the eye may be amaurotic, and hence this symptom is precluded. In the present case there was no history of diplopia.

Most gliomatous tumours of the optic nerve originate in the intraorbital part of the nerve. The rule is that they tend to grow neither into the dural sheath nor into the eyeball. On the other hand they frequently tend to grow backwards through the optic foramen and towards the brain. This tendency leads to widening of the optic foramen, an important sign, which was noted in this case.

Prognosis and Treatment: In spite of the fact that gliomatous tumours of the optic nerve usually develop slowly, the danger of intra-cranial extension exists. Likewise the exophthalmos may become so pronounced as to induce necrosis of the cornea and panophthalmitis.

As these tumours do not as a rule metastasize, radical excision carries a good prognosis. Early diagnosis and adequate removal are important. As these tumours seldom infiltrate the eyeball itself, they may be removed without excising the eye. The usual techniques are those of Lagrange, Knapp and Kroenlein. As all these methods greatly damage the vessels and nerves, subsequent excision of the eye is frequently indicated.

If widening of the optic foramen, suggesting intra-cranial extension of the tumour, is found, or if it is evident that the tumour has been incompletely removed, an intra-cranial operation is advisable (Dandy, 1922; Martin and Cushing, 1923). Before this second operation is done, however, the wound of the first should be healed. This precaution is advised in order to prevent infection and loss of cerebro-spinal fluid. For the same reason secondary enucleation after a cerebral operation must be postponed.

Both Rönne and Duke-Elder are more optimistic in their statements concerning similar cases. Thus Rönne says: " Auf Grund der relativ grossen Benignität der Sehnerventumoren kann das Operationsresultat befriedigend sein, selbst, wo eine völlige Entfernung des Gewebes am Foramen opticum nicht gelingt."

SUMMARY

The case of a 43-year-old woman with a " glioblastoma multiforme " of the optic nerve is given.

The usual symptoms and signs of such a tumour were present. A *widening of the optic foramen was found on repeated roentgengrams*. The tumour was excised together with the bulbus. Unfortunately pathological examination revealed that the operation was incomplete. The patient refused to have a secondary intra-cranial operation. In spite of post-operative X-ray therapy she died one year later from intra-cranial complications.

The pathological picture was characterized by polymorphism, and the diagnosis was " glioblastoma multiforme." The tumour was considered to be primary.

Unusual features in this case were the appearance of the tumour at a relatively late age, its rapid course and its polymorphism.

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AN INCOMPLETE FORM OF MANDIBULO-FACIAL DYSOSTOSIS (FRANCESCHETTI'S SYNDROME)*†

BY

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IN 1944, Franceschetti and Zwahlen (Geneva), after a careful study of the literature, gave a detailed description of two cases of a new symptom-complex affecting the bony structure of the face: mandibulo-facial dysostosis. On studying these cases, it became apparent that a new set of well-defined clinical and anatomical signs was common to all those afflicted with this dysostosis. It is due to Prof. Franceschetti who correlated the symptoms and signs of isolated cases, that the condition is now recognised as a well defined ophthalmological entity.

PRESENT CASE-HISTORY

Julio J., a six-year-old boy, was brought to the out-patient clinic because of a convergent squint. The right eye was convergent (anti-mongoloid type) from birth. The use of spectacles did not reduce the angle of squint. The patient's ophthalmological history was otherwise negative.

FIG. 1.

Front view of the patient.

Eye examination :—

Vision.—R. eye: 0,4 without and 0,6 with correction. L. eye: 0,8 without and 0,9 with correction.

Horizontal deviation: on tangent scale $+50°$; on synoptiscope $+55°$.

Vertical deviation: L. hyperphoria of 30°.

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The patient had abnormal retinal correspondence. A pseudo-von Graefe sign was elicited on the left side.

In short, the eye examination revealed convergent strabismus, contracture of the inferior oblique muscle of the left eye, alternating hyperphoria, pseudo-von Graefe sign on the left, bilateral hypermetropic astigmatism, amblyopia of the right eye. We noticed an asymmetry of the face and a resemblance to previously

FIG. 2.

Right profile view of the patient

FIG. 3.

Left profile view of the patient.

observed cases of mandibulo-facial dysostosis. The right side of the face was particularly suggestive of this condition.

This patient was examined along the lines laid down by Franceschetti and Zwahlen (1944) (Figs. 1, 2 and 3):

1. Palpebral fissures, eyelids, eyelashes: There was an obliquity of the palpebral fissures of 20° on the right and 15° on the left. They measured 30 mm. and 26 mm. on the right and left side, respectively. They were triangular in shape by reason of a downward traction of the external part of the lower lid.

This condition was more prominent on the right. The eyelashes consisted of a double row on the lower lids, and were very long on the upper lids.

2. Upper and lower jaws, palate and teeth: The patient had a superior prognathism and a slightly atrophic, receding chin. The palate had an ogival form (Fig. 4). The implantation of the teeth was very anomalous.

FIG. 4.

The palate of the patient.

FIG. 5.

3. The *malar bones* were atrophic, especially on the right, leading to facial asymmetry.

4. The external, middle and internal ears showed no signs of malformation.

5. The naso-frontal angle was completely absent.

6. No macrostomia or fistulae on the cheeks were seen.

X-ray findings (Figs 5, 6, 7 and 8)

X-ray studies showed a marked facial asymmetry. The anterio-posterior diameter of the cranium was increased (dolichocephaly), and the digitate impressions were large and well-formed. The sella turcica was small and showed very clearly a hyperostosis of the sphenoid bone. The sphenoidal sinus was rudimentary and

FIG. 6.

FIG. 7.

of the hypoplastic type. The frontal sinuses were small and hypoplastic. The mandible also showed hypoplasia. The nasal septum and the vomer were deviated. The palate was in the form of a pointed arch. The orbital perimeter was unequal and orbital asymmetry was evident.

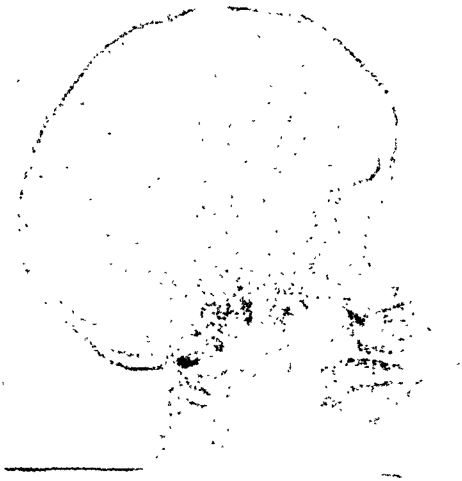

FIG. 8.

General physical and mental examinations

The physical and mental development of the patient were normal for his age. The physical constitution of the patient showed a distinct tendency to the adiposo-genital type.

Summary

The examination of a 6 year-old boy gave the authors the opportunity to describe a case of an incomplete form of mandibulo-facial dysostosis (Franceschetti's syndrome).

It was characterised by:

1. Oblique palpebral fissures and dropping of the lower lids, as well as anomalous implantation of the lashes.
2. Superior prognathism and atrophy of the chin.
3. Atrophy of the malar bones.
4. Ears normal.
5. Complete absence of the naso-frontal angle.
6. No macrostomia or fistulae on the cheeks.

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OCULAR ALLERGY IN HANDLERS OF STREPTOMYCIN *

BY

J. CHARAMIS

ATHENS

THE successful results obtained in the treatment of tuberculosis (particularly tuberculous meningitis) by streptomycin, and the low toxicity of this drug have encouraged its widespread use. Special streptomycin centres have been established, and we apply streptomycin treatment on a large scale. Toxic effects of streptomycin are very few nowadays. This must be attributed to the improved purity of the drug and to the wide experience which has been gained in its use. The toxic effects either involve the nervous system and the organs of the special senses or appear as allergic toxic disturbances.

Dermatitis from contact with streptomycin has been noted, chiefly in physicians and nurses who give many injections daily. Since 1947, first in the United States and later in England and France, studies have been published on pathological appearances of the skin and mucous membrane (conjunctiva) of hospital nurses. The study of such cases has proved that the condition was an allergic manifestation of sensitivity to streptomycin. Contact with the drug is either direct, during its preparation or injection, or indirect, from continuous contact with patients and their bedding.

There is no proof that sex plays any part in the appearance of allergy. Nurses seem to be more often affected because their work brings them into closer contact with the drug and with the patients during treatment. No definite allergic tendency is necessary before the appearance of dermatitis. The intra-dermal tests with weak solutions of streptomycin, administered at frequent intervals to nurses, become strongly positive. This confirms the specific allergic sensitivity as soon as the first cutaneous or ophthalmic (conjunctival) signs appear. This specific drug-allergy appears after a period varying from one to six months of continuous contact with streptomycin.

Sometimes general allergic symptoms such as dizziness, headache and fatigue may be noted. These are followed by the manifestation of dermatitis proper which appears mainly on the hands and face. The eyes and their adnexa are most frequently involved. Varying forms and intensities of blepharitis and conjunctivitis appear. First may come the familiar disturbances of blepharo-conjunctivitis,

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i.e., itching, epiphora and injection of the conjunctival vessels, and blepharitis itching provokes an eczematous dermatitis which may become septic. The conjunctivitis sometimes becomes sub-acute or acute, and the conjunctiva and eyelids are very swollen. Sub-acute or chronic forms of this allergic or professional blepharo-conjunctivitis may be found.

The local treatment should be mild and symptomatic. Chief attention should be given to the avoidance of any contact with streptomycin or with patients receiving streptomycin treatment. The period required for the cure of this benign form of allergic dermatitis is variable. Relapses of completely cured cases of allergic blepharitis and conjunctivitis mean that there has been a fresh contact with the drug.

Since the allergic sensitisation of the skin is not general, the selection of an ophthalmic location may be explained either by the immediate contact of the eyelids (through contamination by the hands) with the solution of streptomycin during preparation or by the exposure of the worker's face to the products of evaporation of the drug. Allergic symptoms in persons working with streptomycin appear to be frequent, and according to present statistics involve from 5 to 57 per cent. of those handling the drug. Some protection may be obtained by the use of rubber gloves and protective goggles.

Many cases of this allergic blepharitis and conjunctivitis have already appeared in the special streptomycin centres, *e.g.*, of 110 nurses and two doctors who administered streptomycin intermittently or continuously thirty nurses (27 per cent.) showed allergic reactions. In 25 of them blepharitis and conjunctivitis appeared, and 22 had also dermatitis on the hands. The other 5 developed only dermatitis on the hands. Nurses who prepared solutions of streptomycin continuously over a long period and had allergic tendencies were more seriously affected.

The most severe of these cases was that of a nurse who had a general allergic tendency, and had prepared streptomycin continuously for two years. After she had been cured a severe dermatitis appeared on her hands and eyelids as soon as she began to work again with the drug; the skin reaction to streptomycin became strongly positive.

In another case of blepharitis and conjunctivitis an extensive dermatitis appeared on the exposed side of the neck.

The intra-dermal reactions to streptomycin in typical cases were generally positive, especially in the most severe and obstinate cases.

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CONTACT SHELL APPLICATOR FOR USE AS A CORNEAL BATH*

BY

M. KLEIN

LONDON

INSTILLED eyedrops disappear from the conjunctival sac within a few minutes (Ridley, 1931/32) and if it is desired that the drug should act for a long time, one has to use it in ointment-form (preferably under bandage) or as a corneal bath. Contact shells are also useful for the local application of drugs to the eye (Klein, 1942), and have proved satisfactory during the past eight years.

The contact applicator looks like a rather heavy contact-lens with two studs on the corneal portion. The scleral part has a diameter

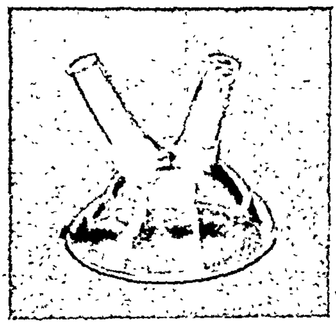

FIG. 1.

of 20 mm. and a scleral radius of curvature of 12 mm. The corneal segment is raised so as to form a chamber for the fluid. The two small studs serve as a handle when inserting the applicator under the lids, and each of them has a bore reaching into the chamber, one for filling up the chamber by means of an eye-dropper, and the other for the escape of air. One drop of half per cent. amethocaine hydrochloride gives sufficient anaesthesia.

To insert the contact applicator the patient is asked to look down, and the upper margin of the contact applicator is slipped under the upper lid. The patient is then told to look up, and the applicator is placed on the eye under the lower lid. Then it is filled up with the solution used for treatment, and the applicator is left in position for the desired period, usually 5 to 30 minutes. If necessary it can

* Received for publication, April 11, 1949.

be refilled. It can be cleaned by washing with soap and water, and chemically sterilized by keeping it in 1:1000 mercuric bichloride or in chlorine solution (Solvellae Chloramine B.P.C. in 4 oz. water) for 15 — 20 minutes, followed by rinsing. Alcoholic solutions, phenolic antiseptics or heat sterilization are not suitable, as they are detrimental to the plastic material of which the applicator is made.

The contact applicator can be used for any solutions such as sulphonamides, mydriatics, miotics, urea, etc. Struble and Bellows (1944 and 1946) have shown that a high concentration of penicillin in the anterior segment of the eye can be built up by the use of a corneal bath, and they have advocated this procedure for the treatment of corneal ulcers, particularly if the deeper layers are involved. In chemical burns the applicator can be used for continuous irrigation with the antidote, such as ammonium tartarate solution in lime-burns. For irrigation a suitably placed flask or undine can be connected with rubber tubing.

The contact applicator is manufactured by Messrs. G. Nissel and Co. Ltd., *Siddons Lane, London*, N.W.1.

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FACULTY TOUR OF ITALIAN CLINICS

UNDER arrangements made by the Faculty of Ophthalmologists, twenty members, led by Dr. Robert Buxton, were able to make a tour of centres of ophthalmology in Italy, the clinics visited being those at Pavia, Genoa, Florence, Rome, Naples and Bologna. At each of these places the hospitality of the professors, and the opportunities for seeing the beauties of their cities, contributed greatly to the enjoyment of what was, in any case, an interesting and instructive tour.

At Pavia the party was welcomed by Professor Bietti and taken to a reception given by the Rector of the University of Pavia. In one of the courtyards of the University is a statue of Scarpa, the first Professor of Ophthalmology of Pavia.

At the Ophthalmic Clinic next morning Professor Bietti showed a number of cases on which keratoplasty had been performed, and demonstrated his technique. He also gave a lecture on Chemotherapy in Tuberculosis. He advised early administration of streptomycin (0·5 gm. b.d. subcutaneously) which may be given with

Promin in a 50 gm. course. He also referred to the use of Para-amino-salicylic acid (P.A.S.), which is well tolerated and rapidly absorbed. The bacteriostatic action of the drug may be obtained by a dosage of 10-15 gm. daily (divided into four doses) given in three week courses; it may be combined with streptomycin therapy. He also gave a second lecture on new trends in diathermy of the ciliary body.

Dr. Malone, First Assistant to Professor Maggiore at Genoa, demonstrated a patient wearing contact lenses with variable curve who was able to see 6/6, 6/9 and also read newsprint without additional correction. A visit was arranged to the San Giorgio Optical Company.

The Ophthalmic Clinic at Florence is a spacious modern building with an extensive out-patient department. Separate accommodation is provided for trachoma cases, but the number is stated not to be large at the present time. Professor Alajmo demonstrated his technique in several operations. He uses no speculum, lid sutures nor superior rectus sutures. Soft lens matter is removed by irrigation with a long-necked undine placed directly in the anterior chamber, the corneal flap being lifted with forceps.

Professor Cavara at Rome, gave a most interesting and instructive lecture on virus diseases of the uveal tract, including a useful classification of the various types. He recommends protein therapy, urotropine and plasma transfusions (especially the latter for sympathetic ophthalmia), using American dried plasma or, preferably, fresh plasma. The first (trial) dose of the latter is 100 c.c. intravenously, after two days 150-200 c.c. Total, five to six doses given at three day intervals. Milk injections have not produced good results.

His second lecture was on streptomycin and P.A.S. He gives 1·0 gm. of the former daily in two to four injections, for twenty to forty days, exceptionally up to sixty days, and observed the results to be satisfactory in twenty-nine cases of uveal tuberculosis, and brilliant in two cases of Parinaud's conjunctivitis. In two cases of choroiditis, one of juxta-papillary choroiditis and two of nodular irido-cyclitis he considered that healing was accelerated. In ocular tuberculosis produced by inoculating rabbits with T.B., he found that whereas streptomycin controlled the infection, P.A.S. had much less effect in checking the disease. The former encouraged fibrotic reaction, the latter cellular. In untreated controls caseation occurred. Professor Cavara then showed a number of cases including a retinal detachment due to cysticercus. This was one of eight cases received from one village, the source of infection being pork. He prefers to extract the cyst through a linear incision through sclera and uvea, which he makes as small as possible to avoid perforating

the retina at the edges of the cyst. Among other cases demonstrated were opacity of corneal stroma in two children, brother and sister, due apparently to congenital absence of Descemet's membrane, congenital atrophy of iris with chronic glaucoma, mobile cysts in anterior chamber following keratoplasty, lacrimation when chewing but not when crying, associated in this instance with Stilling-Turck syndrome, a case of Marcus Gunn's syndrome successfully treated by dividing the levator tendon of the lid and correcting the subsequent ptosis by a modification of Hess's operation, and finally a case of keratoconus, grafted, with the graft remaining flat but the surrounding cornea continuing to stretch.

The assistant professor, Dr. Missiroli, demonstrated his technique in operations for cataract, glaucoma and detached retina.

While in Rome a visit was paid to the Provincial Ophthalmic Hospital, a non-teaching establishment under the care of Dominican nuns. Professor Leonardi demonstrated various different techniques in cataract extraction, including intra and extra-capsular methods, the former with forceps, erisiphake, and diathermy coagulation in turn.

Members of the party will long remember the hospitality afforded to them by Professor Cavara during their stay in Rome, for during unoccupied moments they were not only enabled to see at least some of the famous buildings but also were present at the opera and enjoyed a sumptuous banquet given by Professor Cavara and his wife. Finally, they were honoured by an audience with His Holiness Pope Pius XII.

Much interest was aroused by the demonstrations of operative dexterity given by Professor Lo Cascio of Naples. Using two operating tables and four trained assistants he performed, without any appearance of haste, seven extra-capsular operations in fifty minutes, followed by three cyclodialyses and a diathermy operation for detachment of the retina. The technique he employs in the latter is careful localisation of the hole or holes by indirect ophthalmoscopy, and he inspects the fundus by this method again immediately after applying surface diathermy. The fluid is let out by one or more punctures at the site of the greatest ballooning. He has operated on many hundreds of detachments, and claims 75-80 per cent. successes.

Lastly, at Bologna Professor Di Marzio welcomed the party and gave an address on a subject in which he is particularly interested, that of cranial and cranio-orbital lesions which affect the visual neural paths, with especial reference to the chiasmatic syndrome. He showed records of cases with bitemporal, binasal and homonymous field defects. Slides were exhibited, showing the correlation between field changes and radiological appearances. Most of the

cases were treated with deep X-rays, and the results appear to have been good. (X-ray therapy is much used by Di Marzio in cases of inflammatory diseases of the eye. He gives 100 r. once or twice a week for such conditions as central serous retinitis, ulcerative keratitis and iridocyclitis).

His assistant, Dr. G. Cristini, gave a lecture on the radiographic investigation of obscure lesions of the optic nerves, and described his technique for inserting lipiodol into the paranasal sinuses, and also for injecting thorotrast into the carotid artery for cerebral arteriography.

Apart from the interest and instruction which this tour afforded from the professional point of view, and from the opportunity of seeing some of the most famous of the world's treasures in pictures, sculpture and architecture, no member of the party could fail to be impressed with the evident trouble taken by the various hosts on behalf of their visitors, a debt which it is hoped in some measure to repay here next year. Finally, a word of sincere appreciation for the unselfish and unflagging efforts by the party leader Dr. Robert Buxton, who planned the tour and spared no pains to make it the success it proved to be.

NOTES

Ophthalmological Society of Egypt

IN connection with the recent announcement of an award by the Ophthalmological Society of Egypt it is ruled that this prize is designated only for members of the Society, either in Egypt or abroad, who have been in practice less than 20 years.

* * * *

Appointment

DR. E. V. SRINIVASAN has been appointed Hon. Ophthalmic Surgeon to His Excellency the Governor General of India.

* * * *

Ophthalmological Society of Australia

MR. J. H. DOGGART and Mr. T. K. Lyle have been elected Honorary Members of the Ophthalmological Society of Australia.

THE BRITISH JOURNAL OF OPHTHALMOLOGY

DECEMBER, 1949

COMMUNICATIONS

INVESTIGATIONS INTO HYALURONIC ACID AND HYALURONIDASE IN THE SUBRETINAL FLUID IN RETINAL DETACHMENT, PARTLY DUE TO RUPTURES AND PARTLY SECONDARY TO MALIGNANT CHOROIDAL MELANOMA

Preliminary Report Suggesting a New Hypothesis Concerning the Pathogenesis of Retinal Detachment*

BY

ERIK GODTFREDSEN

COPENHAGEN

INTRODUCTION

ALTHOUGH Meyer and Palmer isolated hyaluronic acid 15 years ago (1934), it was Chain and Duthie's discovery (1940) that the "spreading factor" is identical with hyaluronidase, the enzyme depolymerizing hyaluronic acid, which gave an impetus to the study of these biological substances. Hyaluronic acid constitutes

* Received for publication, July 21, 1949

an important element of a number of the refracting media of the eye, and it is only natural that various valuable ophthalmological papers dealing with this substance should already have been published. Thus investigations have been made into hyaluronic acid in the cornea, the aqueous humour, the crystalline lens (Meyer 1938, 1940, and 1948), and the vitreous body (Pirie *et al.* 1948, Pirie 1949). But no investigations into hyaluronic acid in the subretinal fluid are available.

The object of the present investigation has been to test the subretinal fluid for hyaluronic acid as well as hyaluronidase for the purpose, if possible, of throwing some light on the numerous problems regarding retinal detachment. Demonstration of the presence or absence of these substances in the subretinal fluid may perhaps contribute to the elucidation of the pathogenesis of retinal detachment (the question of the share which the vitreous body has in the subretinal fluid), its diagnosis (serous detachment *versus* secondary detachment in malignant melanoma from the choroid, or in exudative retinopathy); and furthermore, its prognosis (chance of healing after surgical diathermy). Last, but not least, it may open new vistas for supplementary medication with antihistamines.

Before proceeding to the present investigations I shall briefly recapitulate the results of investigations by other writers, as well as modern views concerning:—

(1) the nature of the subretinal fluid; (2) the vitreous body; and (3) hyaluronic acid and hyaluronidase, with the main stress laid on conditions of importance for the following discussion. It is outside the scope of the present work to enter further on these subjects, of Egypt it may be referred to the comprehensive text-bmembers of the Society the most recent articles in the been in practice less than 20 y

DETACHMENT

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harmonizes with the theory that the main site of production of normal vitreous body is the pigmentary epithelium.

The passage of vitreous body *via* the retinal rupture is easily envisaged in cases displaying large ruptures at the ora, but these are rare. In detachment after small or even minimal ruptures it is more difficult to understand how vitreous body could penetrate, though indeed liquefaction of the latter may totally change the possibilities of transfer (see later).

If a retinal rupture is demonstrable—and careful examiners can nearly always find one—the subretinal fluid is relatively clear, yellowish, mucous and ropy, and it does not coagulate on standing. Where the detachment is of longer duration the albumin content will increase, possibly under the influence of transudation from the vessels of the choroid. In cases of very long-standing detachment the albumin may altogether disappear simultaneously with atrophy of the choroid (Duke-Elder). The part of the vitreous body which penetrates subretinally will undergo certain successive changes and become admixed with heavy water and protein from the choroid (Weve and Fischer 1940).

If the retinal rupture is *not* demonstrable (in these cases it is hardly a question of primary serous detachment, but rather of exudative retinopathy—whether locally induced or of systemic origin), then the subretinal fluid is highly coagulable, jelly-like, grey and albuminous, often with admixture of blood. This finding is analogous to inflammatory exudates in other parts of the organism.

In cases of malignant melanoma of the choroid the subretinal fluid is highly albuminous. The albumin yields the special yellowish colour visible on ophthalmoscopy (Ronne 1936). Adequate physico-chemical analyses of the subretinal fluid are missing in these cases.

In serous detachments analyses of the subretinal fluid have revealed great variations in the albumin concentration (about 135 - 60 per cent.), sugar values as in the vitreous body, and a chloride concentration differing from that of blood plasma (Duke-Elder). Jasiniki has made viscosity tests (1933). The following enzymes have been demonstrated: amylase (Weve and Fischer 1937) and acetyl-cholinesterase (Weve and Fischer 1939).

THE VITREOUS BODY

The vitreous is not, as previously believed, of a cellular nature, but a gel comparable to a mass of plasma (Davson 1949). If the water is evaporated " residual protein " will remain, together with the polysaccharide hyaluronic acid—the latter being a

protein-free substance erroneously called mucoprotein in the past. These two non-haematogenous substances determine the special structure of the vitreous body (Pirie 1948 and 1949), in which the high viscosity is due to hyaluronic acid. The hyaluronic acid is responsible for 30 per cent. of the organic weight of the vitreous body (Meyer 1948).

Recent comprehensive analyses made on frozen sections of vitreous body showed in several respects a chemical resemblance to the aqueous humour (Duke-Elder and Davson 1949), but there was a great difference with regard to phosphate content (Palm 1948).

The vitreous body has been demonstrated to contain the following enzymes: amylase, proteinase, and acetyl-cholinesterase (Uvnäs and Wolff 1938). The action of these enzymes is *accelerated by change of pH in the acid direction, and an autolysis* may take place. Liquefaction of the vitreous body may also occur through haematogenous enzymes, notably hyaluronidase, which (see below) specifically depolymerizes the hyaluronic acid into low-molecular reducing agents.

Hyaluronic Acid and Hyaluronidase

Hyaluronic acid (Meyer and Palmer 1934) is present in the *ground substance of connective tissue, the jelly of Wharton in* the human umbilical cord, the synovia of joints, and abundantly in the vitreous. Smaller amounts exist in the cornea, aqueous and crystalline lens, but not in blood and cerebrospinal fluid. Chemically hyaluronic acid resembles the anticoagulant heparin. It is a high-molecular polysaccharide, a polymer of a disaccharide consisting of glucuronic acid and N-acetyl glucosamine (a hexosamine). The molecular weight has not been finally settled. *It depends on the degree of polymerisation*, but is within the range of 200,000 to 500,000. The hyaluronic acid, probably produced from the cells of the connective tissue (type not yet elucidated), presents as a mucous, highly viscid fluid. The high viscosity conditions the resistance of connective tissue (and other tissues) to passage of both corpuscular elements (bacteria, Indian ink particles) and liquefied substances (toxins, snake venom, etc.).

The enzymatic depolymerisation of the hyaluronic acid is due to the specific enzyme *hyaluronidase* (Chain and Duthie 1940), which is identical with the "spreading factor" previously demonstrated in extracts of testis, malignant tumours, snake venoms and bacterial cultures (Hofman and Duran-Reynals 1930, McClean 1930). Hyaluronidase is prepared from bull semen and is a high-molecular substance, which has not yet been produced in pure form. Addition of hyaluronidase to a viscid hyaluronic

acid solution will cause a prompt depolymerisation of the hyaluronic acid into glucuronic acid and glucosamine, and the fluid will now become thin like water. The depolymerisation of the high-molecular hyaluronic acid into the low-molecular reducing disaccharides may in part be followed viscosimetrically, and partly by the power of reduction.

The sites of production of hyaluronidase are, in cases of infection, the bacterial elements, and, in cases of malignant tumours, presumably the supporting elements of the tumour tissue. Mayer and Kull (1947) have shown that an allergic tissue reaction, *e.g.*, within a skin area, will involve local production of hyaluronidase, which, by its influence on the hyaluronic acid of the connective tissue, contributes to the allergic process—in this instance spreading of oedema. Mayer and Kull succeeded in inhibiting the hyaluronidase activity by antihistamines (pyribenzamine). This opens new prospects for our understanding of the allergic process and the possibility of supplementary therapy.

A quantitative estimation of hyaluronic acid is still difficult. Such is based partly on viscosimetry (Meyer; Dalgaard-Mikkelsen and Kvorning), and partly on reduction determination of the reducing depolymerisation products. The relation of viscosity to quantity is not yet elucidated. Hyaluronidase is estimated biologically by its effect on the hyaluronic acid, partly *in vitro* (viscosimetry) and partly *in vivo* by the rate of spreading of Indian ink particles injected subcutaneously.

PRESENT INVESTIGATIONS

The series on which the present investigations are based comprises 17 patients with retinal detachment, whose data appear from Table 1. Some of the patients were admitted to the Kommunehospital and some to the Rigshospital, Copenhagen. There were 9 females and 8 males ranging in age from 16 to 65 years. *The retinal detachment* had the following *causes*: direct trauma in five cases (1, 2, 3, 4, 5), excessive myopia in five cases (6, 7, 8, 9, 10), uncertain or unknown cause in another five cases (11, 12, 13, 14, 15), of which, however, case 15 presented a generalized exudative disease: Besnier's prurigo with simultaneous syndermatotic cataract. In two cases (16, 17) the retinal detachment was secondary to a histologically verified malignant choroidal melanoma.

The extent of the retinal detachment is indicated in retinal squares, from one-fourth to four-fourths with the following distribution: two cases one-fourth (9, 13), seven cases two-fourths (1, 3, 5, 8, 11, 12, 16), three cases three-fourths (6, 7, 10), and finally five cases total detachment (2, 4, 14, 15, 17); thus a representative series.

TABLE I—The relative viscosity of the subretinal fluid in 17 cases of retinal detachment

Case No.	Sex Age	Retinal detachment: Etiology	Size in squares	Tear	Duration in mths	The subretinal fluid: Relative viscosity	Hyaluronidase	Comments
1	F.-25	Traumatic	2/4	?	12	1·30	—	
2	M.-39	—	4/4	+	1	1·30	—	
3	M.-51	—	2/4	+	1	1·20	—	
4	F.-46	—	4/4	+	1½	1·50	—	
5	M.-49	—	2/4	+	1/10	1·00	—	1940 I detachment Now 1949 re-operation
6	M.-46	Excessive yopia	3/4	?	2	1·30	—	
7	F.-43	—	3/4	+	1	1) 1·40 2) 1·10	— —	1) from the bulk + tear 2) from the bulk — tear
8	F.-54	—	2/4	+	1/10	1·20	—	
9	F.-44	—	1/4	+	1/2	1·10	—	
10	M.-29	—	3/4	+	1	1·10	—	Total detachment in the other eye previously
11	F.-23	questionable	2/4	—	?	1·30	—	
12	F.-65	?	2/4	+	1	1·30	—	
13	F.-62	?	1/4	+	3	1·30	—	
14	F.-50	?	4/4	+	18	1·10	—	Case of re-operation
15	M.-16	Besnier's Prurigo	4/4	—	?	1·0	—	Generalized exudative diathesis affecting the skin, etc., + cataract syndermatotica. Re-operation.
16	M.-50	Melanoma malignum choroid	2/4	—	1	1·0	—	
17	M.-35	—	4/4	—	8	1·0	—	

Retinal rupture was definitely found in thirteen cases, and suspected in two others. Rupture was not observed in four cases, of which two with melanoma and two of an exudative character (cases 1 and 15), the latter the one with Besnier's prurigo. The ruptures were in all cases rather small. Some were of the ordinary horse-shoe type, while others were of the cribriform, cystoid type. None of the cases presented disinsertion or large rupture at the ora serrata.

The *durations of the retinal detachments* were as follows: less than one month in three cases (5, 8, 9), one to three months in nine cases (2, 3, 4, 6, 7, 10, 12, 13, 16), and from three to eighteen months in three cases (1, 14, 17). In two cases the duration could

not be fixed (11, 15). The retinal detachment was treated by ordinary surgical diathermy (according to Larsson-Weve), except in the two cases with malignant melanoma, where enucleation was performed. Course and result will not be discussed here. During the operations the subretinal fluid flowing through the scleral perforations was collected and placed in a refrigerator. Possible admixture of larger or smaller amounts of blood proved to play no great part for the further investigation, since blood contains no hyaluronic acid.

The subretinal fluid was then tested as soon as possible for hyaluronic acid and hyaluronidase in the Department of Pharmacology, University of Copenhagen. These tests were performed by the *viscosimetric technique* recently elaborated by Dalgaard-Mikkelsen and Kvorning (1948). Although the method, the details of which appear in the original article, is a sensitive micromethod, a dilution of 1 in 10 of the subretinal fluid was chosen in the majority of the cases, in order to obtain a sufficiency of material for examination. The procedure consisted of placing the diluted, subretinal fluid in the specially constructed viscosimeter, where, at a constant temperature, the duration of flow through a capillary tube with a given lumen was measured in seconds. Three or four control measurements were made. The flow-time for distilled water is 80 seconds, but for diluted subretinal fluid flow-times up to 120 seconds have been noted. In the cases where the flow-times exceeded that for distilled water a little hyaluronidase was added to the solution, and then, after a few minutes' standing, another series of readings was taken. This brought about prompt reduction in the flow-time, *e.g.*, from 120 to 90 seconds. The relative viscosity was calculated on this basis, and the values have been set out in Table 1.

The changes observed in the flow-times after addition of hyaluronidase can be due only to the fact that the previously viscid solution has changed its character in consequence of the depolymerisation of the hyaluronic acid. If the genuine, subretinal fluid presented flow-times approximately corresponding to that for distilled water, so that we may exclude the presence of hyaluronic acid, the solution was *tested for hyaluronidase* content by addition of a known standard solution with hyaluronic acid.

In a small number of cases there was occasion to determine the relative viscosity of both undiluted and diluted (1 :10) subretinal fluid. To give an idea of the reduction of the relative viscosity brought about by dilution it may be stated that relative viscosity 1·3 in dilution 1 :10 corresponds to relative viscosity 4·0 in undiluted fluid. As, however, the present investigation aims only at a preliminary qualitative estimation, these facts will not be

discussed further. They will be dealt with in greater detail in future papers.

The *relative viscosities in the subretinal fluid* were as follows:

In the five cases of traumatic origin: 1·20-1·50 in four cases, and 1·0 in one case (5) (re-operated on).

In the five cases with excessive myopia: 1·10-1·40. In one case (7) the value was much higher in a sample from the site of rupture (1·40) than in one from another part, where no rupture was found (1·10).

In the five aetiologically uncertain cases: 1·30 in three, 1·10 in one (14) of re-operation, and 1·0 in one (15) presenting Besnier's prurigo.

In the two cases of malignant choroidal melanoma: 1·0.

Since relative values of 1·10 or more are suggestive of the presence of hyaluronic acid, it appears that *hyaluronic acid was found in all the cases of serous detachment*, except two submitted to re-operation (5 and 14), and one of exudative retinopathy as part of a generalized exudative disease (Besnier's prurigo). Hyaluronic acid was *absent in both cases of malignant choroidal melanoma*.

Hyaluronidase was demonstrable *in none* of the 17 cases.

Regarding the relation of the duration of the retinal detachment to the amount of hyaluronic acid, estimated approximately on the basis of the relative viscosity, it appeared that the highest relative viscosities—and thus the highest hyaluronic acid values—were found in the cases of 1 to 3 months' duration. The cases of shorter and those of longer duration, on the other hand, presented lower relative viscosities, such comparatively small material must be cautiously interpreted.

There appears to be a definite correlation between retinal *rupture and relative viscosity*, since hyaluronic acid was present in all cases of rupture, except those re-operated on owing to recurrence, where special conditions asserted themselves.

Discussion

Although the present investigation is based on a rather small number of cases of retinal detachment, the results of the hyaluronic acid analyses in the subretinal fluid are fairly uniform. It appears that in primary, serous, retinal detachment the subretinal fluid contains considerable amounts of hyaluronic acid, which are responsible for the characteristic ropy and mucous character of the fluid. In cases of malignant choroidal melanoma with secondary retinal detachment, on the other hand, the subretinal fluid is not viscid, and hyaluronic acid could not be demonstrated. In two cases of recurrent detachment and one of

exudative retinopathy as part of a generalized disease (Besnier's prurigo) no hyaluronic acid was found.

The fact that such large amounts of hyaluronic acid were demonstrated in all the cases of primary serous retinal detachment with ascertained retinal rupture bears out the hypothesis advanced by previous writers (Weve and Fischer) that the subretinal fluid comes from the vitreous body, the considerable hyaluronic acid content of which has been established (Pirie, Meyer). The fact that the hyaluronic acid concentration in the subretinal fluid seems small at first, and then gradually increases, may contribute to an understanding of the pathogenesis.

Our knowledge regarding retinal rupture and retinal detachment is still scanty, despite the enormous work done by various investigators in their attempts to find the factors giving rise to the lesions. The results of the present hyaluronic acid investigations as well as recent discoveries concerning the liberation of hyaluronidase by allergic vascular or tissue reactions (Mayer and Kull) are of such a nature that it may be tempting, on the basis of them, to *set up a new hypothesis with regard to the pathogenesis of retinal detachment.*

The cases where the pathogenesis is evident, *i.e.*, the traumatic detachments (after perforating injuries, etc.) will here be left out of account. The trauma will often present the character of a triple-response reaction (Lewis-Ebbecke), having many features in common with the allergic vascular reactions.

In other cases of retinal detachment, where direct physical trauma is absent, it may be of value to search for possible psychic trauma in the past history. The possibility of a psychosomatic origin of a disease is gaining ground within many branches of medicine, thereby explaining to an increasing extent why mental conflicts may often give rise to complicated somatic symptoms, presumably *via* certain diencephalically released angioneurotic lesions. The " general adaptation syndrome " recently described by Selye in both physical and mental " stress " likewise contributes to greater clarity. Many eye diseases (glaucoma, iridocyclitis, relapsing superficial keratitis, scleritis, detachments, etc.) of obscure origin may thus be elucidated and explained in a new manner.

Since hyaluronidase is liberated by allergic vascular reactions —as shown by Mayer and Kull—it is reasonable to suppose that an analogous *angioneurotic vascular lesion*, in a portion of peripheral retina, for instance, may cause similar liberation of hyaluronidase. The primary vascular lesion in the retina will involve a *local ischaemia* with consequent tissue necrosis, resulting in *cystoid degeneration*, which sooner or later will *develop into a*

rupture. The liberated *hyaluronidase* within the ischaemic area will *depolymerize the hyaluronic acid* in the adjacent vitreous body, the high viscosity of which will thereby become reduced. The attenuated *vitreous body* may now pass through the retinal rupture. The extent to which the vitreous body *penetrates sub-retinally*, thereby conditioning the development of retinal detachment, depends no doubt on various factors. A certain balance will occur between the two portions of the vitreous body on both sides of the retinal detachment, and the depolymerization of the hyaluronic acid will stop. Consequently—as demonstrated in the present analyses—we find a somewhat higher hyaluronic acid concentration in cases of more long-standing detachment.

The hypothesis here advanced needs further testing on several points. If it proves possible to apply Mayer and Kull's neutralisation of hyaluronidase, successfully carried out in the skin with antihistamines, to the problem of retinal detachment we may thereby have a chance of supplementing with a causal therapy our current operative treatment, the results of which, as is well-known, are of limited value and merely symptomatic.

Whether we may be justified in drawing certain conclusions with regard to the result of the surgical diathermy treatment on the basis of estimation of the hyaluronic acid concentration in the subretinal fluid is a question which cannot yet be definitely answered. It will be discussed further in a future paper.

In cases of retinal detachment, where an underlying malignant melanoma in the choroid is suspected, we may sometimes fail to reach a definite clinical diagnosis by our present diagnostic aids. The present *hyaluronic acid investigations* suggest that, by analysis of subretinal fluid procurable by simple test puncture, we have obtained a new *differential-diagnostic aid for classification* of the uncertain cases where *malignant tumour* is suspected, because hyaluronic acid is *not* present in the subretinal fluid in cases of malignant melanoma.

Absence of hyaluronidase in the two cases of malignant melanoma does not necessarily exclude the fact that hyaluronidase may have been present at previous stages of the tumour proliferation, as is known from other malignant tumour proliferations. That the violently metastasizing melanomata may be supposed at a certain stage to possess a large hyaluronidase activity is a possibility which requires further investigation.

Summary and Conclusions

The main features of our present knowledge concerning the nature of the subretinal fluid in retinal detachment, the vitreous body, and the recent biological discoveries of hyaluronic acid and

hyaluronidase are recapitulated. This is followed by a report on present investigations into *hyaluronic acid and hyaluronidase in the subretinal fluid in retinal detachments*, partly primary with ruptures and partly secondary as a consequence of malignant choroidal melanoma.

Hyaluronic acid and hyaluronidase have been estimated viscosimetrically. In all cases of *detachment with retinal ruptures the subretinal fluid contained a considerable amount of hyaluronic acid*, which, on the other hand, was absent where the detachment was secondary to choroidal melanoma. Hyaluronidase was demonstrated in *none* of the cases.

These observations have prompted a *new hypothesis concerning the pathogenesis of retinal detachment.* The development is now conceived to take place gradually by a primary, vascular retinal ischaemia producing cystoid degeneration with rupture formation. and associated with partial liquefaction of the vitreous body. The *liquefaction is caused by local liberation of hyaluronidase*, which in turn produces partial depolymerisation of the hyaluronic acid in the vitreous body.

Tests for hyaluronic acid in the subretinal fluid may become of differential diagnostic importance in difficult cases of malignant melanoma with extensive secondary retinal detachment and small primary tumour.

Hyaluronic acid analyses may become prognostically directive for the diathermal treatment of retinal detachment. Since hyaluronidase may be inactivated by antihistamines (Mayer and Kull) the possibility of a supplementary causal treatment with these substances is suggested.

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CHOROIDAL SARCOMA WITH METASTASIS IN THE OPPOSITE ORBIT*

BY

SEYMOUR PHILPS

LONDON

THE history here recorded is that of a woman who, ten years after enucleation of one eye for choroidal sarcoma, developed an encapsulated metastasis in the opposite orbit.

HISTORY

In February, 1938, a lady, aged 59 years, attended the Royal Westminster Ophthalmic Hospital because the right eye had become red and painful. The sight had been failing for a year in this eye, and was only perception of light. She was found to have glaucoma secondary to a large choroidal sarcoma, and the eye was removed (see Fig. 1). Microscopic section confirmed the diagnosis (see Fig. 2).

At this time her left eye was normal, and its corrected vision 6/6. She continued to attend the hospital, but no recurrences arose, and she remained in normal health. Apart from the periodical replacement of her glass eye, nothing unusual happened for nine years.

April, 1947. The patient had an attack of iridocyclitis in the left eye which cleared up completely in one month.

May, 1948. It was found that, whereas the patient had worn a correction of $-2{\cdot}0$ sph./$+0{\cdot}5$ cyl. at 90° with which she saw 6/6, her refraction had now changed, and she achieved normal vision with a $+0{\cdot}5$ cyl. at 90°. While this drop of 2 dioptres of myopia was noted, there was nothing to account for it, and the patient had no complaint, being pleased that her vision had so improved.

October, 1948. The patient noticed that the left eye appeared to be coming forward, and reported to hospital. The proptosis was straight forward, and there was no limitation of movement. This proptosis was variable, and in the following month seemed less marked. X-rays of the orbit revealed no bony changes and the fundus and vision remained normal.

* Received for publication, June 27, 1949.

December, 1948. The proptosis was rather more marked, and a dilated vein appeared in the conjunctiva at the outer canthus. Abduction was slightly limited, and by deep pressure between the globe and the outer bony wall of the orbit a vague resistance could be felt.

It was decided that the left orbit must be explored, and she was told to attend hospital the following week so that she might be admitted, the diagnosis being a tumour behind the left globe, possibly a metastasis.

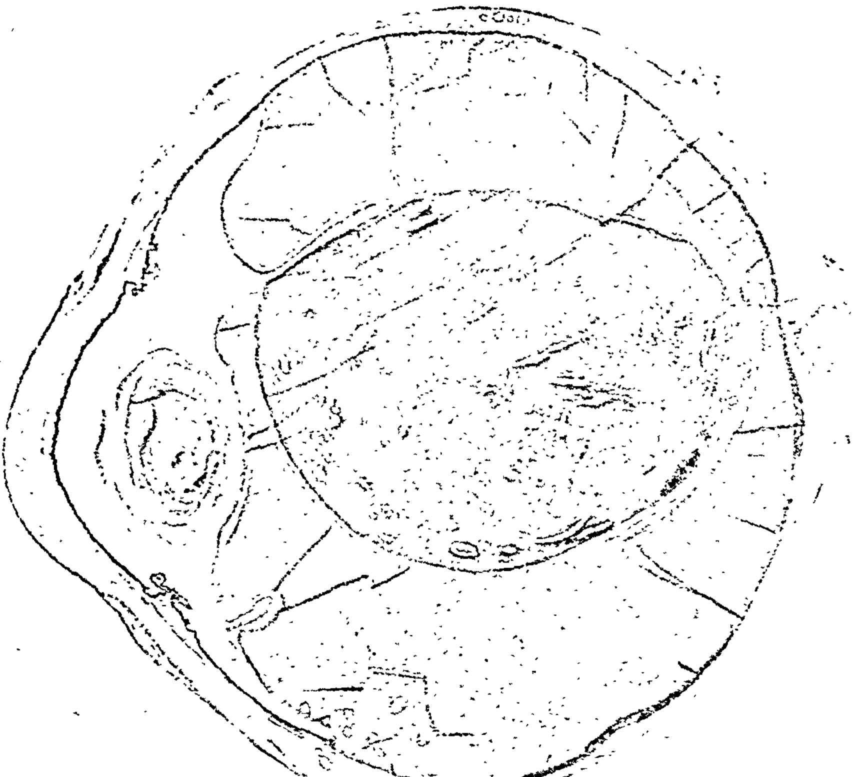

FIG. 1.

Photograph of right eye excised in 1938, showing a large malignant melanoma of the choroid.

The day after this decision had been taken her doctor telephoned the hospital to say that she had been taken acutely ill with a sudden alarming proptosis of the left eye, the cornea of which was exposed so that the lids would hardly meet. She was admitted at once, the diagnosis being haemorrhage into a retro-ocular neoplasm, and the house surgeon performed an emergency tarsorrhaphy.

The swelling and congestion of the left eyelids and orbital tissues remained for three weeks, but, as no blood-staining of the eyelids occurred, the diagnosis of haemorrhage into the orbit seemed less probable, though it was still felt that the bleeding might have occurred into an encapsulated tumour.

January, 1949. Three weeks after admission a left lateral orbital exploration was carried out (Kronlein's exposure), and an encapsulated tumour was found lying within the muscle cone and attached to the under side of the external rectus muscle. After reflexion of this muscle the tumour came away quite easily except at the apex of the orbit, to which it was attached by fibrous tissue which had to be divided. The capsule was accidentally punctured at one stage in the removal with escape of necrotic material, so that a dermoid cyst seemed the most likely diagnosis at this stage. For photograph of tumour see Fig. 3. The position of the tumour is shown in Fig. 3A.

The patient made an uneventful recovery and left hospital nineteen days after operation. Fig. 4 shows the operation scar just before leaving hospital. At that

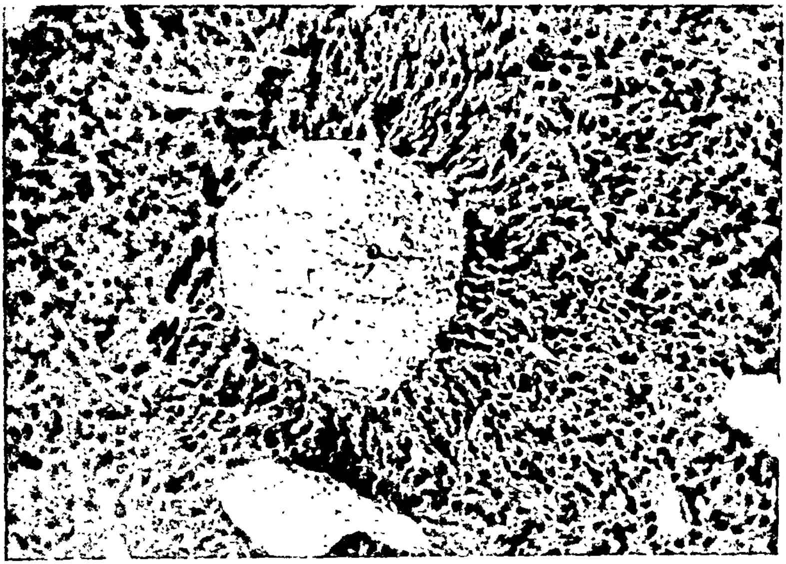

FIG. 2.

Photomicrograph of the malignant melanoma of the choroid (right eye) removed in 1938. Note the perivascular arrangement of the spindle cells—compare with Fig. 3. H and E. × 306.

time the left vision with −1·0 sph. was 6/6 partly, but one month later she was a little more myopic, and it is interesting to note the return of her myopia when the pressure behind the eye was relieved. She has remained in good health and vision since that time, her vision at this date (June, 1949) being once more, with −2·0 sph.,/ +0·5 cyl. at 90°, 6/6.

PATHOLOGY.—By Dr. Norman Ashton, Pathologist to the Moorfields, Westminster and Central Eye Hospitals.

Left Orbital Tumour. Pinkish-yellow, ovoid, soft, encapsulated tumour measuring 2·4 cms. × 1·25 cms. × 1·5 cms. (Fig. 3).

Sections. A series of sections taken from different parts of the tumour were stained with haematoxylin and eosin, Van Gieson's stain, Wilder's silver stain and Masson's trichrome stain. Frozen sections were stained with Sudan 111. The

tumour is bounded externally by a dense fibrous capsule, containing voluntary muscle fibres, which merges insensibly with the cellular mass which forms the bulk of the tumour (Fig. 5). Centrally the lesion is completely necrotic, and between the zone of necrosis and the fibrous capsule there is a margin of large polyhedral vacuolated cells supported in a loose fibrous stroma infiltrated with lymphocytes (Fig. 6). In the frozen section stained with Sudan III these cells are seen to contain globules of fat. In the Masson-stained section the structure of the central necrotic area is clearly discernible, and is seen to consist of masses of spindle cells, which are aggregated as a mantle around the thin-walled blood-vessels, with their long axes arranged radially (Fig. 7). Silver staining shows dense pericellular reticulin formation around the large peripheral cells (Fig. 8), but only a few filaments remain within the necrotic area. A small quantity of intra- and extra-

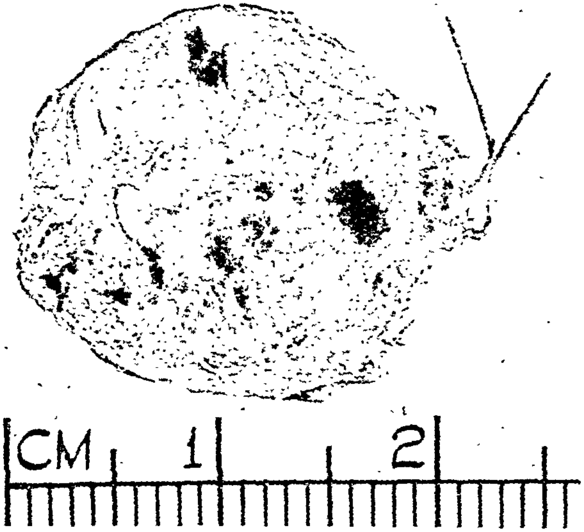

FIG. 3

cellular pigment is present in the living cell layer. The appearances in the necrotic zone are typical of a malignant melanoma of the choroid, and a comparison with the histology of the tumour of the right eye removed 11 years previously (Fig. 2) leaves little doubt that the orbital tumour is in fact a metastasis from the original growth. The border of large fat-containing cells might be regarded as an inflammatory reaction to the central necrotic mass, but it appears more probable, from a study of the margin of the living and dead tissue, that the whole lesion was originally composed of the same type of cell. In 1912 Ginsberg described three cases in which lipoid degeneration was found in melanotic growths of the choroid: fat was deposited within the cytoplasm of the spindle cells, so distorting and distending them as to form large "foam cells" which, judging from his illustrations, are identical with those in this case. In my view, therefore, this tumour is an encapsulated malignant melanomatous metastasis arising from a primary in the choroid of the right eye and undergoing central necrosis and peripheral lipoid degeneration.

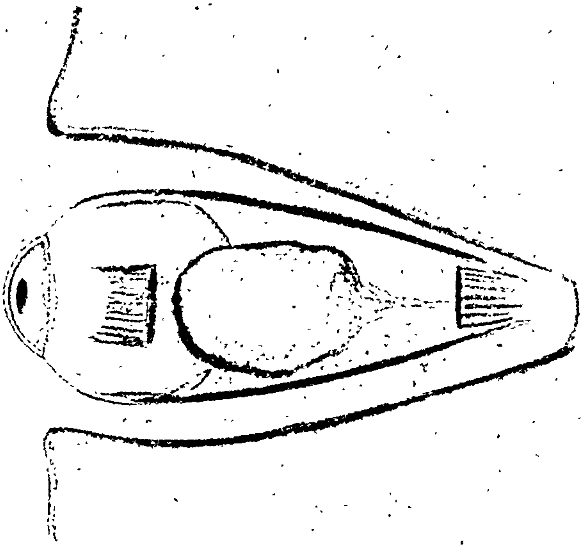

FIG. 3a.

Site of growth within the muscle cone of the L. orbit.

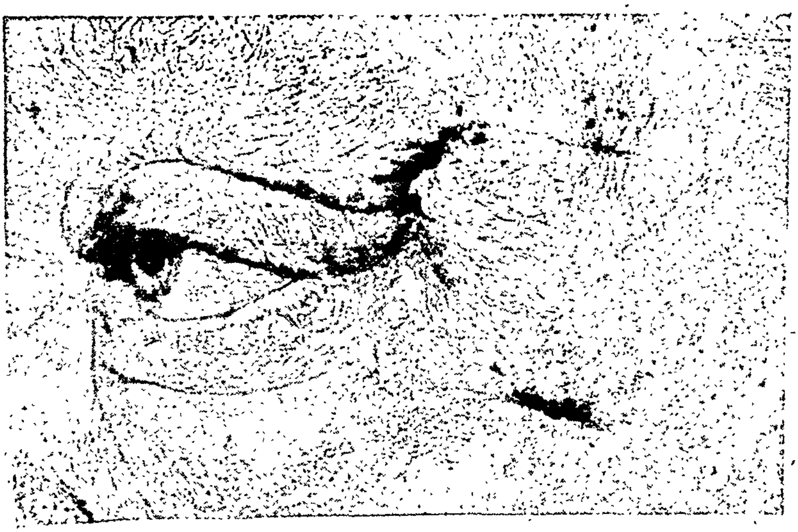

FIG. 4.


HAMBLIN'S ALL PLASTIC
ARTIFICIAL EYES
WILL BEAR CRITICAL
INSPECTION
THEODORE
HAMBLIN LTD
DISPENSING OPTICIANS
15 WIGMORE STREET
LONDON, W.1

FIG 5.

Photomicrograph of orbital tumour. From left to right can be seen the fibrous capsule containing muscle fibres, the zone of large fat-containing cells and the central necrotic mass of spindle cells. Masson stain × 130

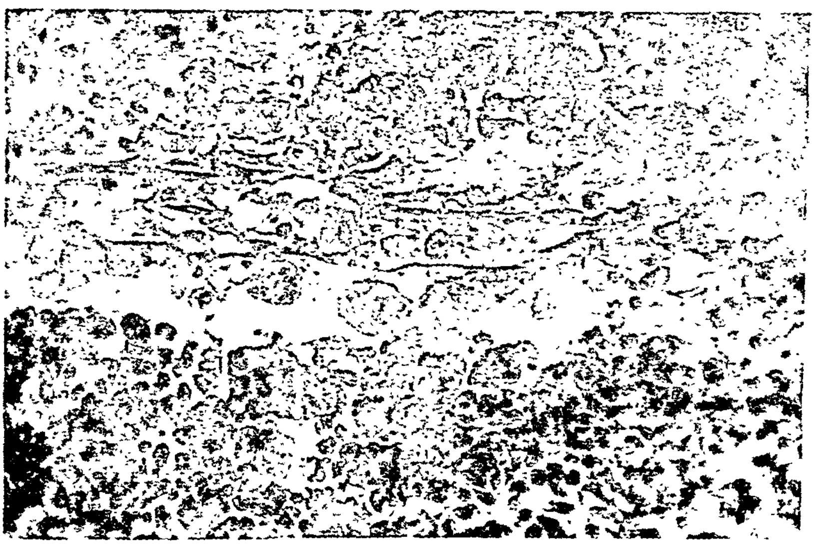

FIG. 6.

Photomicrograph showing the junction of the necrotic tissue below with the margin of large fat-containing cells above. Masson stain. × 410.

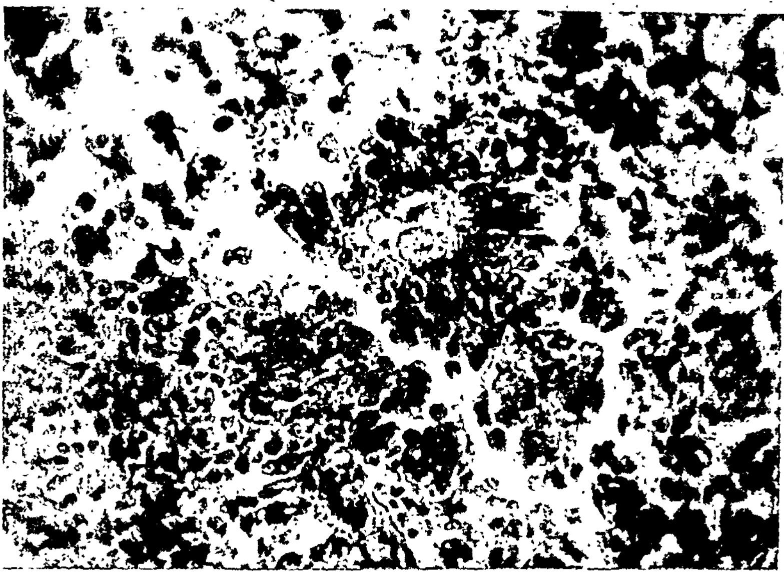

FIG. 7.

Photomicrograph of the central necrotic area showing spindle cells arranged radially around the blood vessels. Compare with the photomicrograph of the original tumour (Fig. 5). Masson stain. × 410.

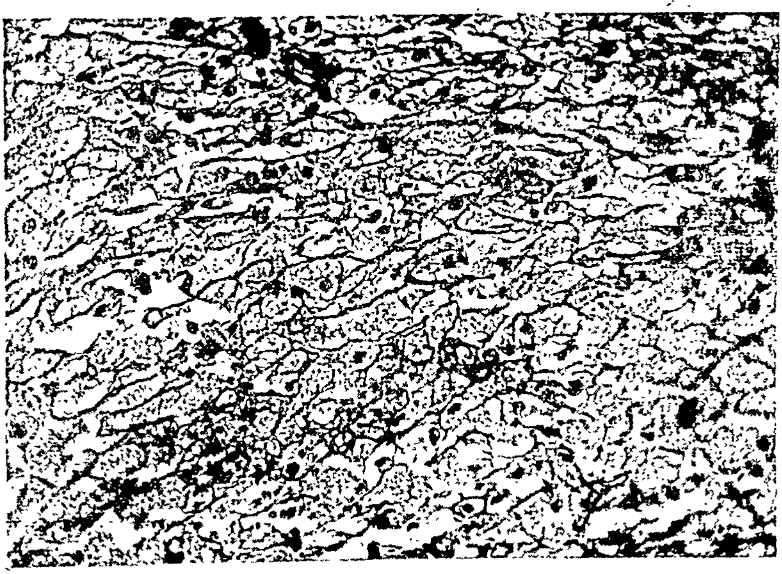

FIG. 8.

Photomicrograph showing pericellular reticulin formation around the large peripheral cells. Wilder's silver stain. ×410.

Conclusions

No instance has been discovered in the literature of a history such as is recorded here, of a woman surviving a large choroidal sarcoma for 10 years, then developing a metastasis in the opposite orbit, which being encapsulated could be completely removed leaving normal vision.

I am grateful to Dr. [illegible] for [illegible] he has taken over this tumour, and to Dr. [illegible] of the Medical Illustration Department of the Institute of Ophthalmology for his fine photographs.

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HISTO-PATHOLOGICAL STUDIES OF THE BLOOD-VESSELS OF THE EYE*

BY

R. SYSI

HELSINKI

THERE are numerous publications in the literature dealing with arteriosclerotic vascular changes in the eye. Most of them are based on a comparatively small material which explains the diverging opinions on many points. Thus Koyanagi, Friedenwald and lastly Bergstrand consistently noted more conspicuous changes in choroidal vessels than in those of the retina, while Rintelen observed marked vascular changes in the retina only in few cases. He rarely found any considerable changes in the a. ciliares posteriores, while the others found pronounced sclerosis therein. Rintelen denies the existence of any severe sclerosis in the blood-vessels of the iris and the corpus ciliare, in contrast to Gasteiger and, more recently, Rones, who found great changes in these vessels. There are also differences of opinion as to whether the sclerotic changes spread as far as the anterior parts of the choroid and the retina, or whether they occur only nearer to the posterior pole of the eye. These examples will suffice to show that further studies on vascular changes in the eye are not out of place.

* Received for publication, June 1, 1949.

From the Patho-Anatomical Institute, University of Helsinki.
Chief: Professor Arno Saxen, M.D.

Research workers have as a rule discussed the condition of the eye vessels and their changes in cases of general arteriosclerosis, renal diseases such as nephritis, nephrosclerosis, etc., or when vascular sclerosis of the brain has been present at the same time, but no comparative study has been made of the age-changes occurring in the ocular blood-vessels, when there is no general sclerosis nor any marked local sclerosis in other organs. Thus it is these so-called normal cases that show general wear-and-tear in the vascular system with advancing years.

It was the effect of renal disease in impairing vision that first drew the attention of physicians to the close connection between ocular blood-vessels and those of the rest of the organism (Bright). Clinical experience proved later that many other diseases may give rise to vascular lesions in the eye. Only a few of these ocular changes caused by various general diseases or affections in some other organ come within the scope of the present investigation. Some of these changes we consider physiological, others are on the borderline of the pathological. Some of them occur irregularly, occasionally even in comparatively young individuals, sometimes no traces of them are found even in advanced age, such are gerontoxon, atrophy of the iris and miosis, retinal and choroidal changes, concentric or partial contraction of the visual fields, etc. In other changes, however, such as failing accommodation, we note strict regularity, for this diminution begins in early childhood and nearly always follows the same time-table, to such an extent that a person's age may be determined with considerable accuracy from his accommodative capacity.

Some of these changes must obviously be ascribed to arteriosclerosis. Others again, occurring where there is no arteriosclerosis present, can be explained by changes and wear caused in the tissues by age. A corresponding phenomenon may be noted in many other organs, notably in the blood-vessels. The occurrence of this phenomenon in the blood-vessels does not, however, mean that the wearing-out of the tissue results from vascular changes, but rather that both phenomena arise from the same fundamental cause at the same time, but independently of each other.

When beginning to study the blood-vessels of the eye it is advisable first to note the changes which occur normally in otherwise healthy individuals, before we tackle the question of strictly pathological, arteriosclerotic phenomena. I have therefore collected an extensive control material of cases where no general arteriosclerosis or renal diseases have been diagnosed. Both series have been collected, treated, studied and evaluated in similar circumstances and according to the same principles.

The material studied was taken from 204 corpses, and consists of 408 eyes. The preparations were obtained by dividing the eyes in front of the equator and taking the whole posterior part of the eye with the orbital part of the optic nerve and the surrounding tissue. From the anterior part of the eye the parts within the cornea and sclera were removed for study by detaching them with a spatula, as in the operation of cyclodialysis. The preparations thus include all parts of the eye except the cornea and the 4-5 mm. wide anterior part of the sclera. The preparations were fixed in formalin and stained by van Gieson's method and with elastin. Part of the preparations were also cut with a freezing microtome and stained for fat. We have full clinical records of all the cases, and all the corpses had also been fully dissected.

The distribution of the cases into a control series, arteriosclerotic cases without hypertension, nephritic cases and cases with nephrosclerosis, and into different age groups appears from the following table :—

TABLE 1

Age	0–15	16–30	31–40	41–50	51–60	61–70	71–80	81–90	Total
Control cases	7	9	11	17	22	10	—	—	76
Arteriosclerosis	—	—	—	5	6	6	5	3	25
Nephrosclerosis	—	—	—	7	17	31	17	5	77
Nephritis	1	3	6	4	6	3	3	—	26
Total	8	12	17	33	51	50	25	8	204

Several investigators have noted what was found by us in studying the present material—namely, that the blood-vessels of the eye are subject to the same pathological changes as occur elsewhere in the organism. In different parts of the eye these changes take place with varying intensity and in different relations to each other. Opinions vary in the literature as to what, and how great, changes occur in different parts of the eye. It is therefore not out of place to give a short account of these changes as they appear in the present material.

The optic nerve has two kinds of blood-vessels, first, the central retinal artery and vein which pass through the nerve, and secondly, the small pia and septum arteries providing for the nutrition of the nerve itself.

Great changes of the intima are observable in the *arterioles* of the optic nerve, also homogenization and thickening of the wall, and, more often than anywhere else in the eye, complete hyalinization and obstruction of the blood vessel.

In the arteries of the retina, extensive proliferation of the intima and fatty change, also homogenization of the vascular wall occur. In the elastica there are no marked changes. Considerable thickening and increase of the number of nuclei is often noted in the adventitia. In the smallest vessels the changes are especially frequent in the intima. One generally finds that the changes are most

obvious in the retinal parts nearer the papilla, and that they grow less farther away from it. Yet one sometimes notices such changes even in the outermost retinal arteries.

A. ciliares posteriores, which are relatively large blood-vessels, show all these changes in the vascular walls. Besides changes in the intima, severe proliferation of the elastica, delamination and muscular hypertrophy are found. The only actual instance of atheroma occurred in these vessels, and completely obstructed blood vessels are not infrequent.

In the large blood-vessels of the choroid, besides intimal proliferation and fatty change, severe proliferation and delamination and thickening of the muscularis and the adventitia sometimes occur. Changes in the intima and fibrosis are noted in the small vessels, sometimes homogenization. As in the retina, the greatest changes take place in the posterior parts of the eye, but there is less difference in the choroid between the anterior and posterior parts.

In the *corpus ciliare* and in the *iris* the changes are usually slight. Some intimal changes occur, and also fibrosis and homogenization. Here it is more difficult to estimate the changes than elsewhere, since the general hyalinization of the tissues, which sometimes takes place, makes it difficult to distinguish the actual vascular wall from the surrounding tissue. In the iris vascular changes are generally still smaller than in the corpus ciliare. Yet even in the blood-vessels of these organs there is sometimes quite obvious sclerosis.

As well as in cases with arteriosclerosis, changes of this kind occur in the control series, where they must be regarded as normal for every age-group. We know that such changes occur in various parts of the vascular system from childhood, according to recently published statistics on general sclerosis, 8 per cent. in 0-9 year-olds and 23 per cent. in 10-19 year-olds (Eskola).

In the various groups the changes do not differ from each other qualitatively, but they certainly do quantitatively. All parts of the eye have this in common that, when changes occur, their intensity varies greatly even in the same region, so that one finds, side by side, healthy and diseased blood-vessels.

On first comparing the different groups and age-groups one finds that the quality of the changes is easy to estimate exactly, but there are no clearly defined standards by which we can measure the quantity of the changes nor any formula by which they can be expressed exactly, but one has to be satisfied with one's personal observations as regards the intensity of the phenomena and its relation to a change observed in some other vessel.

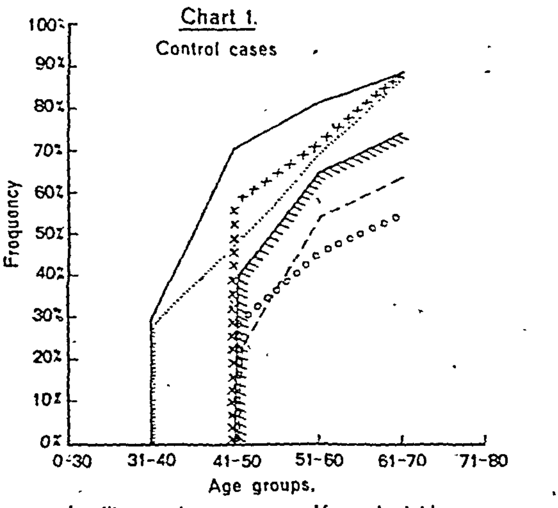
The number of control cases in the material which show no hypertension, no noticeable arteriosclerosis and no renal lesion is 76 (Table I). Their ages vary from new-born to 70 years.

Under 30 years no vascular changes have been observed in the eyes of the cases in this control series (Chart 1). The changes begin to appear between 31 and 40, and then first in the a. ciliares posteriores and the arterioles of the optic nerve, and even in these in somewhat over a quarter of all the cases. In the next age group, 41 to 50, changes appear in all vascular areas. They are still most frequent in a. cil. posteriores and after that in the blood-vessels of the choroid and in the arterioles of the optic nerve. There are fewer changes in the other regions, least of all in a. centr. retinae and in the blood-vessels of the corpus ciliare. In the following age groups the frequency of the changes in the a. ciliares posteriores, in the vessels of the choroid, and in the arterioles of

the optic nerve increases regularly, reaching about 90 per cent. in the age group 61-71, but being much less in the other groups.

Thus, in the control cases the changes occur most frequently in a. ciliares posteriores, in the choroid, and the arterioles of the optic nerve. It is in these vessels, too, that among the cases examined the changes are clearest and greatest. In other regions, *i.e.*, in the retinal vessels and the corpus ciliare and in the a. centr. retinae the changes are slight. This relation between the intensity of the changes in the different areas is typical of these control cases, where there is no general sclerosis or renal lesion.

Also qualitatively the changes in the control series show special features. The changes mostly occur in the outermost parts of the vessels. In a. ciliares posteriores especially the muscularis and the adventitia thicken, but also the elastica interna may show some thickening though no delamination. The vascular



changes in the choroid are likewise unmistakable, but here also mainly in the outer parts. Fibrosis and homogenization occur to some extent in the smallest vessels. In a. centr. retinae one meets only very slight thickening of the muscles and of the adventitia, and in the small vessels of the optic nerve one may find some homogenization. The changes in the blood-vessels of the retina and the corpus ciliare are extremely slight.

In the material there were 25 cases of arteriosclerosis without hypertension in the 40-90 years age groups (Table 1). General arteriosclerosis occurred in 11 cases, in 19 cases the sclerosis was most advanced in the valves, vessels, and aorta of the heart. It should be noted that the material includes 9 cases with obvious sclerosis of the cerebral blood vessels. The sclerosis in the different organs varied from mild but clearly obvious to the most severe forms.

As regards the vascular changes in the eye we note that their frequency, when compared with that of the former group, is slightly larger (Chart 2). Only in the highest age group, 81-90 years, do we here reach the 100 per cent. limit. This does not mean that patients of this age with arteriosclerosis always had changes in all the vascular regions of the eye, since the number of cases in this group is only 3, which is too small a number for conclusions. This is quite apparent from the following Chart (No. 3), showing a group of cases with

Chart 2.

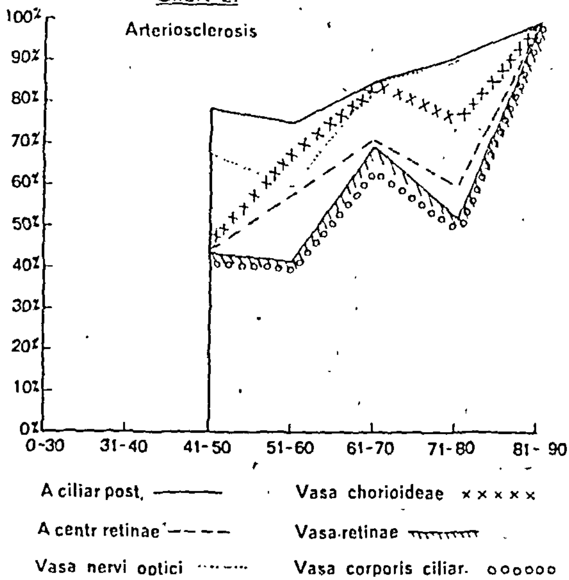
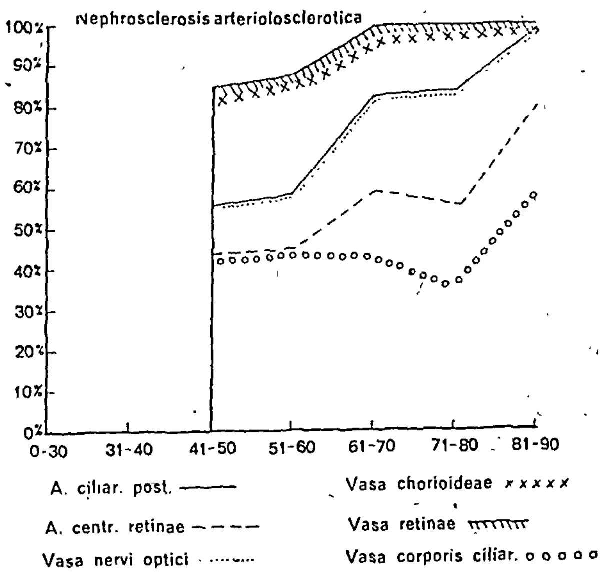


Chart 3



nephrosclerosis, where even in the highest age group there were some without any changes in the blood-vessels of the corpus ciliare and the a. centr. retinae.

In this chart as in the former, the curves divide into two groups. The curves representing the a. ciliares posteriores, the arterioles of the optic nerve and the choroid together rise high above the others, while the three other curves, forming a group of their own, are much lower. The interrelation between the frequency of changes in the different vascular areas within the group of arteriosclerotic cases is roughly the same as in the control material. The frequency of the changes in the cases with arteriosclerosis is slightly higher in the younger age-groups than in the control cases, but then the rise is less steep. Thus there is no great difference ascertainable in the frequency of the changes between these groups.

The difference in the quality of the changes, on the other hand, is remarkable. Besides the changes noted in the control cases, which were most marked in the outer-most parts of the vessels, intimal changes now become clearly discernible. All the changes are more pronounced and greater than in the preceding group. In the a. ciliares posteriores one can see relatively marked proliferation of the elastica and evident delamination. The changes are most intense in the arterioles of the optic nerve and the choroid, but there is not yet any delamination to speak of in the latter. In a. centr. retinae, in the retina and in the corpus ciliare the changes are still mostly rather small, but with a few exceptions, where rather severe sclerosis occurs.

Although general arteriosclerosis was the rule in the other blood-vessels of the organism in this group of cases, there were several in whom the changes differed neither in quality nor in quantity from those in the same age-groups of the control series.

In this group there were 9 cases of vascular sclerosis of the brain. The relation of this disease to retinal vascular sclerosis must be investigated on the basis of these cases, since in the following group with nephro-sclerosis there is the complication of another disease which may affect the retinal blood-vessels. 6 out of 9 cases in our series had vascular changes in the retina and 7 in the choroid. In two cases, of which one was as old as 72, both the retinal and choroidal vessels were normal.

The number of nephrosclerotic cases in the material is 77 (Table 1), and their age varies from 41 to 90 years. All these cases showed according to the case record a considerable rise in blood pressure, varying between 170 and 280 mm. Hg. In this group the frequency of the changes (Chart 3) was from the first greater in the retinal and choroidal vessels than in the earlier groups. In the other vascular regions, on the other hand, the frequency was approximately the same as in the earlier groups. In the higher age groups the frequency of changes in the choroidal and retinal vessels rose rapidly to 100 per cent. In the others the course of the curves was approximately the same as in the previous ones, and as far as the vessels of the corpus ciliare and the a. centr. retinae are concerned it was lower than for cases with arteriosclerosis.

The grouping of the curves has thus changed. The curves of choroidal and retinal vessels form a group in themselves, with the greatest frequency of changes. Since this fact may give a misleading picture, it is especially important to point out how variable in quantity the changes are. This group contains 4 cases in which the changes are no greater, in any part of the eye, than the changes in quality or quantity occurring in other cases of the same age group. There are, in addition, 3 cases in which the vascular changes in the retina may be placed in the same group as the arteriosclerotic cases of the same age.

Although there is wide divergence in the severity of the changes, they have on the whole increased considerably, especially in the retinal vessels. Pronounced changes are also observed in other vascular regions, but the difference compared with earlier age-groups is smaller in them than in the retina. In other regions,

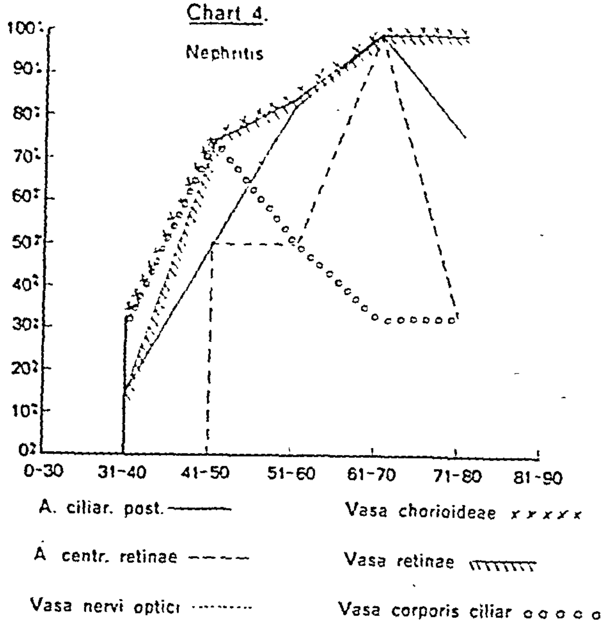
too, the variations in the severity of the changes in the same vascular region are considerable. Both great changes and almost intact blood-vessels may be found everywhere.

The most important difference compared with earlier groups is the remarkable increase in the severity of the vascular changes in the choroid and in the retina while the increase is smaller in other vascular regions. Other authors, and quite recently Bergstrand, have pointed out that in these cases the changes in the choroidal vessels are more severe and occur earlier than vascular changes in the retina. This phenomenon was also obvious in the present material, but with exceptions to the rule in so far as there were certain cases of choroidal changes which fell far below those in the retina in intensity. Yet since there has been no series of excisions on the eyes for investigating this particular point, the apparent exceptions may be due to the fact that the intensity of the changes also varies at different points of the same vascular region.

In the vessels of the corpus ciliare and in the iris the changes are still usually slighter than in other parts of the eye, but this group contains cases where they are conspicuous. As regards the quality of the changes, it is the same as before in this group, but the various types of changes now appear more strongly and clearly. Usually all the layers of the vascular walls are involved in the process. Intimal proliferation, fatty changes, proliferation of the elastica and delamination, thickening of the muscularis and the adventitia are not very pronounced. We even find in the a. ciliaris posterior of a 49-year-old case the only instance of actual atheroma.

In the a. centr. retinae we find changes in all layers of the wall, but they are usually slight. Only rarely was the intima markedly thickened and the elastica delaminated. The arterioles of the optic nerve show relatively great intimal proliferation and one often meets hyalinization and even complete obstruction of the vessel. In the choroid all layers are affected by the process, and the present material contains cases where the elastica also is strongly delaminated, although this phenomenon is otherwise rarer in these vessels than elsewhere. The smallest vessels show advanced homogenization and hyalinization, and obliterated vessels are not uncommon. In the retinal vessels we find marked fatty changes and changes in the adventitia. There are other less obvious changes. The difference between these changes and those observed in earlier groups is so great that it is only in this group that one can speak of unmistakable changes. This does not rule out the existence of obvious changes earlier, but they are not common until we reach this group.

There were 26 nephritic cases (Table 1), and their ages varied from 18 to 80. This group is very heterogeneous and difficult to estimate. Indeed, the group contains cases whose ages vary greatly, cases without diagnosable sclerosis, and cases of severe general sclerosis. All these factors in themselves affect both the picture of the single cases and the frequency chart (Chart 4). The number of the cases is, however, so restricted that to separate the arteriosclerotic cases would mean breaking up the group entirely. Thus all the cases have been treated together, which fact should be kept in mind when estimating the general picture. From a critical point of view we may, however, point out that in this group the changes mostly occur in the vessels of the retina and the choroid and in the a. ciliares posteriores, and they are also frequent in the arterioles of the optic nerve. In this respect the curves have roughly the same course as in nephrosclerosis. However, the greatest frequency occurs in a younger age group than in nephrosclerosis.



The quality of the changes is much the same as earlier, but with this difference that now, besides the changes already mentioned, evident oedema is in some cases observed in the outermost parts of the vessels, which appears as a swelling of the wall, which stains imperfectly. This sign is clear even when no other actual changes are observable.

In the 41-50 years age-group we found retinal vascular changes in the control material as well as in the arteriosclerotic cases. Nephritic cases had changes in the earlier age group, both oedema and fatty changes of the intima. But my material is so small—there are only 4 in the 0-30 age group, and 6 in the 31-40 years group—that we cannot say conclusively that there may not have been changes earlier than in the 31-40 years age group. On the other hand, as even the control series is rather small with 16 in the group 0-30 years and 11 in the age group 31-40, we cannot consider that it sufficiently proves the absence of retinal changes in groups younger than 41-50 years, without actual sclerosis having been diagnosed elsewhere, and with no renal disease present. It therefore still remains open to question whether the changes were actually caused by nephritis. The oedema in the vascular wall may perhaps be considered as an actual nephritic change.

From the facts recorded above, the following points may be emphasised :—

The changes in the control material are slight, occurring mainly in the outermost parts of the blood vessels, and take the form of adventitial and medial thickening, slight fibrosis and sometimes homogenization, rarely slight thickening of the intima, and fatty change.

In connection with arteriosclerosis the changes are usually more obvious, though some cases do not differ from those in the control group. The real difference compared with the control material

is that in arteriosclerosis the changes generally occur in the whole wall and are obvious in the media and also in the intima. *Not until arteriosclerosis develops* do we find severe proliferation of the elastica, and delamination. Complete hyalinization and obstruction of the vessels occurs sometimes. Atheromatous foci occurred *only in one case*.

In the quality of the changes nephrosclerotic cases do not differ essentially from cases with arteriosclerosis, but changes are more easily discernible. Nephritic cases have, in addition to the changes mentioned above, oedema in the vascular wall.

The changes both in the control material and in other groups first involve the arterioles of the optic nerve and the a. ciliares posteriores, and afterwards the blood-vessels of the choroid. Changes are rarer in a. centr. retinae and in the retina, and are not demonstrable until severe arteriosclerosis develops. Both retinal and choroidal changes first occur posteriorly, but are occasionally found in *the anterior regions of the retina and the* choroid. Changes are less frequent in the vessels of the corpus ciliare and the iris than elsewhere in the vascular system of the eye. Thus, though the locality of the changes varies considerably and some vascular areas in the eye are obviously more prone to damage than others, *we may say that changes can occur in* all the blood-vessels of the eye.

The extent of the changes seems to depend upon where they occur. *Generally they seem to be greatest where they appeared* earliest, *e.g.*, in the a. ciliares posteriores, in the arterioles of the optic nerve and in the choroidal blood-vessels. The most conspicuous changes were found in the a. ciliares posteriores, which *harboured the sole instance of atheroma. In the corpus ciliare and* the iris the changes are usually slight.

In all parts of the eye the amount of change varies considerably. Blood-vessels close to each other may differ greatly, one being *intact, the next severely damaged,* although both belong to the same vascular region of the eye. Likewise the changes *vary considerably* between different vascular areas. On the other hand there is no marked disparity between the blood-vessels of the left and the right eye.

There is one exception to the rule that the greatest changes occur where they appear earliest, in the mild cases, namely, the changes in the blood-vessels of the retina. In the control cases and *in mild cases of arteriosclerosis the retinal changes follow the* rule mentioned above, but in more severe sclerosis, nephrosclerosis, and in nephritic cases the changes in the retina are noticeably greater than those elsewhere.

This change in interrelation is especially obvious when the state of the retinal blood-vessels is compared with that of the vessels in the choroid in different groups. In the control cases and in mild sclerosis we find changes in the choroidal blood-vessels without there being anything pathological in the blood-vessels of the retina. Changes in the retinal vessels are always less than those

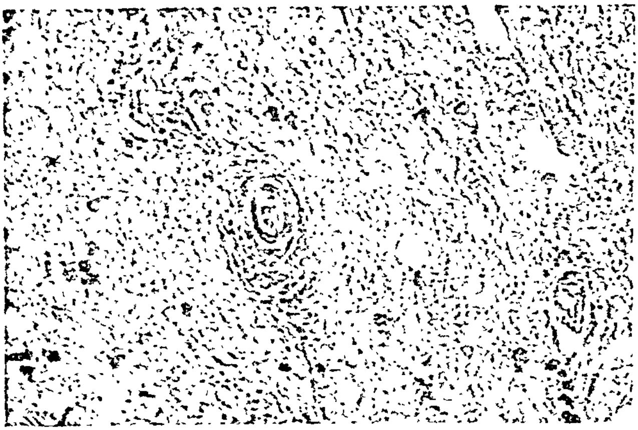


FIG. 1.

Thickening of the wall of an arteriole of the optic nerve.

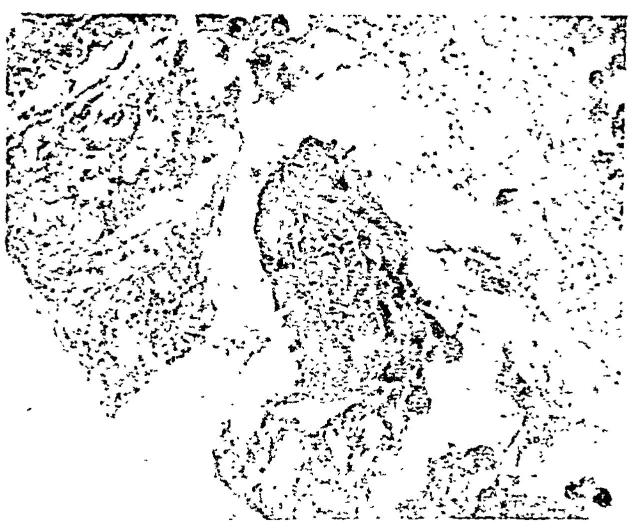


FIG. 2.

Thickening of the wall of a retinal vessel.

in the choroid. On the other hand, in more severe cases of sclerosis, nephrosclerosis and nephritis, the vascular changes in the retina may equal those in the choroid.

FIG. 3.

Thickening of the wall of a small retinal vessel.

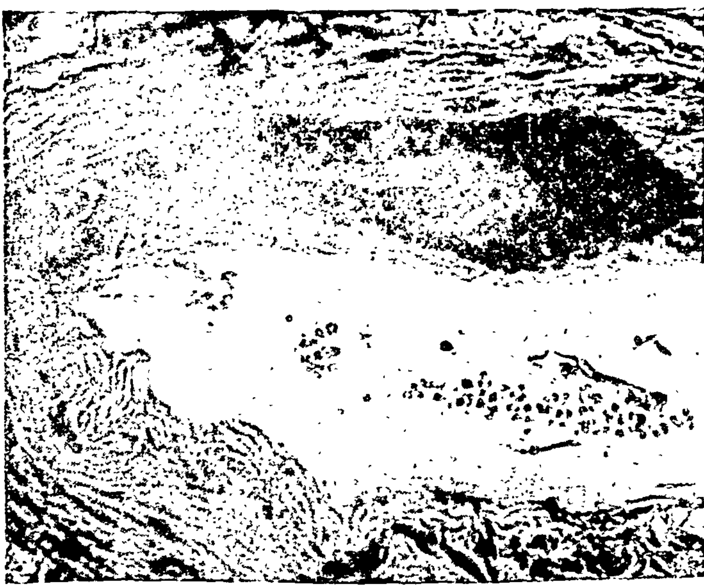


FIG. 4

Atheroma in the wall of an arteria ciliaris posterioris.

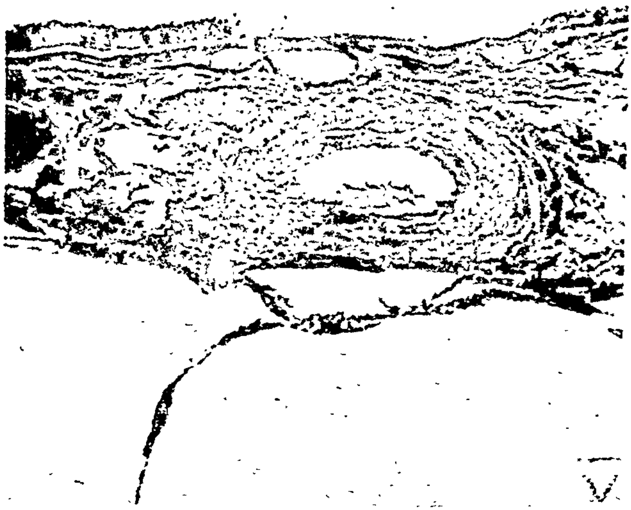


FIG. 5.
Fibrosis of a vessel of the choroid.

FIG. 6.
Obstruction of a vessel of the choroid

FIG 7.

Fibrosis and hyalinisation of the vessels of the ciliary body.

FIG. 8.

Hyalinization of the vessels of the iris.

Concerning the frequency of the occurrence of the changes, we notice that in the present material they begin to appear after the age of 30, and the incidence then increases evenly. In the group of normal changes and in cases with arteriosclerosis the curves (Charts 1 and 2) divide into two fairly distinct groups, of which the curves of the a. ciliares posteriores, the arterioles of the optic nerve and the curves of the choroid form the upper group, while the frequency curves showing vascular changes in the a. centralis retinae, the retina and the corpus ciliare run in a separate group lower down.

When we come to the groups of nephrosclerotic cases and those with nephritis, we have a different grouping of the curves (Charts 3 and 4). It is the retinal changes that now show the greatest frequency and the corresponding curve has the highest peak. In the a. centralis retinae and in the blood-vessels of the corpus ciliare the frequency of changes remains relatively low in all groups. A renal lesion does not seem to have any appreciable effect on these vessels. As to diabetes, which is known to cause changes in the pigment epithelium of the iris (*Deutschman, Kamochi*), the present material does not warrant any conclusions, for it contains very few cases of diabetes.

From a comparison between the results derived from the present material and those recorded in the literature we would make the following points. In contrast with Rintelen we find frequent and great changes in the a. ciliares posteriores. Nor can we agree with his theory that changes are rare and usually small in the region of the corpus ciliare. My material seems to support the view of many other authors, *e.g.*, Gasteiger, Mylius and Rones, that considerable changes are found here.

My series also supports the findings of Koyanagi, Friedenwald and Bergstrand that severe sclerosis occurs in choroidal blood-vessels. The material contains some severe cases of nephrosclerosis in which the vascular changes in the choroid, though pronounced, are yet slighter than those noted in the retina. We also note, as did Rintelen, Bergstrand and others, that sclerosis of the retinal vessels may extend as far as the ora serrata, though Mylius had earlier declared that sclerosis is limited to the posterior retina.

The oedema in the vascular wall, found in cases with nephritis, supports Wagener's statement that it is possible to differentiate between the retinopathy of glomerular nephritis and that of essential hypertension. On the other hand we find that even arteriosclerotic changes are relatively frequent in the blood-vessels of the nephritic group.

My material also supports Volhard's statement that the retina reflects the condition of the kidneys. Advanced changes in the retinal blood-vessels imply the existence of similar changes in those of the kidney, but healthy vessels in the retina are not proof against disease in the renal blood-vessels. Raehelmann's theory that the blood-vessels of the retina reflect the condition of the cerebral blood-vessels has earlier been disproved, and is further contradicted by the present material.

Summary

The material consisted of 408 eyes taken from 204 corpses. It was divided into four parts: the control series, including those cases in which no clinical signs of sclerosis had been recorded, cases with arteriosclerosis, those with nephrosclerosis, and nephritic cases.

The changes noted were always comparatively slight in the a. centralis retinae. In the arterioles of the optic nerve, on the other hand, we found extensive changes, and these blood-vessels were often obstructed. The changes were likewise considerable in the a. ciliares posteriores, wherein atheroma and frequent obstruction occurred. The third region where the changes were often extensive was the choroid. The vascular changes in the retina were as a rule slight in the control material and in cases with arteriosclerosis, while in the nephrosclerotic cases and sometimes in nephritic cases they were more pronounced. Vascular changes occurred even in the anterior parts of the retina. The changes were usually slight in the blood-vessels of the corpus ciliare and the iris.

The changes were of the type usually occurring in sclerosis, with the exception of the oedema in the vascular wall which was noted in nephritic cases.

Among the control cases and those with arteriosclerosis, the frequency of the changes was greatest in the arterioles of the optic nerve, in the a. ciliares posteriores and in the blood-vessels of the choroid. In cases with nephrosclerosis and nephritis the greatest frequency occurred in choroidal and retinal blood-vessels. In the control material the frequency of the changes did not exceed the 90 per cent. limit even in the oldest age-groups.

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CONVERGENCE*

An investigation into the normal standards of age groups

BY

A. MELLICK

GLASGOW

A SURVEY of the literature reveals that there is considerable discrepancy as to the normal values of the horizontal ductions of the eyes. Table I analyses the results obtained by various authorities. It will be seen that the results vary widely, and difficulty is encountered in explaining these divergent findings. Unfortunately comparison between the conclusions of different observers is rendered difficult, since in many instances no mention is made of the type of instrument employed, or of the kind of target used.

The present investigation represents an attempt to establish the normal range of ductions. For this purpose, the following procedure was adopted.

TABLE I.—*Duction Values by Various Observers*

Figures are in prism dioptres

Author	Abduction		Adduction	
	Distance	Near	Distance	Near
A. Græf		5-10		30 or more
Berens, Losey and Hardy ...	6	16 19	16	38-41
C. Sheard				30
M. Dobson	8	18	24	30
Weymouth, Brust and Gobar		17		20
S. V. Abraham		21		19
G. H. Giles	7-8	16-18	24	24
L. C. Peter	4-8		15-18	
N. A. Stutterheim			50	
J. Maxwell				18
Scobee and Green			19	

Certain criteria were essential in the selection of cases. It was in the first place, necessary to exclude any subject who suffered from gross ocular disease. The material was derived from the outpatients of the Glasgow Eye Infirmary, and the major portion consisted of those who had been treated for, and had recovered

* Received for publication, July 14, 1949.

from, such minor disabilities as conjunctivitis and chalazion. The residual group comprised those who attended for correction of errors of refraction, provided the latter did not exceed 4 dioptres of hypermetropia or myopia. Furthermore, the presence of heterophoria rendered the individual unsuitable for inclusion in the survey. The group, accordingly, cannot be taken to represent a complete cross-section of the community, but it does offer a reasonable basis for the object in view. The effect of age obviously merits special study, and accordingly the results have been analysed in terms of age groups.

A wide variety of instruments for testing ductions is available. Broadly speaking, these utilise one of two principles. One type is based on the principle of applying gradual increase of prism power, and is represented by the variable prism stereoscope. In the second type of instrument, two fused images are separated or approximated by rotating the slide-carriers of the synoptophore. Both principles were adopted, so that comparison of the results of the two groups could be obtained, each patient being tested with the variable prism stereoscope and the synoptophore.

The possible influence of the nature of the target requires further investigation, but in the present study, use was made of only two targets. One was a simple flat fusion target, and the other was a stereoscopic target of the bucket type. With the variable prism stereoscope, the target at distance was a letter of the 6/6 or 6/9 line of Snellen type; while at near, the line of letters on the Sheard card was employed. For measuring the ductions at distance with the stereoscopic target using the variable prism stereoscope, the pictures were placed in the instrument with +3·00 dioptre lenses in the eye-pieces, and these were removed for measuring the corresponding ductions at near.

Measurements were taken after the existing error of refraction had been corrected. The inter-pupillary distance of each patient was measured, the distance phoria was read on the Maddox tangent scale, and the Maddox wing was used for measuring the near phoria. Examination of the subject was completed with one

TABLE II

Distribution of patients in age-groups

Age	0-20	21-30	31-40	41-50	51-60	61+	Total
Number	115	128	96	116	53	53	561

instrument before testing with the other, the variable prism stereoscope usually being first employed. In the event of any persistence of convergence after measurement of adduction, sufficient time was allowed to permit of relaxation.

Observations were made on 561 subjects. The numbers in the respective age groups are shown in Table II.

TABLE III.—*Variable Prism Stereoscope*

ABDUCTION

Mean Values and Standard Errors

Prism Dioptres

Measures	Age 0-20 years	Age 21-30 years	Age 31-40 years	Age 41-50 years	Age 51-60, years	Age 61+ years	All Ages
D1 ...	8·2±0·2	8·2±0·3	7·8±0·3	7·8±0·2	7·9±0·3	7·5±0·3	7·97±0·10
D2 ...	9·0±0·4	8·6±0·4	8·5±0·4	9·2±0·3	9·7±0·4	9·5±0·3	9·09±0·15
N1 ...	13·2±0·3	13·8±0·4	13·7±0·4	13·9±0·3	14·3±0·5	12·6±0·5	13·61±0·16
N2 ...	11·7±0·3	11·9±0·3	12·7±0·4	12·3±0·3	11·8±0·4	11·7±0·4	12·04±0·15

TABLE IV.—*Variable Prism Stereoscope*

ADDUCTION

Mean Values and Standard Errors

Prism Dioptres

Measures	Age 0-20 years	Age 21-30 years	Age 31-40 years	Age 41-50 years	Age 51-60 years	Age 61+ years	All Ages
D1 ...	18·0—0·6	17·0±0·6	16·6±0·6	18·1±0·6	17·8±0·7	19·5±0·8	17·68±0·26
D2 ...	17·8±1·7	16·5±1·0	16·0±1·4	18·2±1·1	18·9±1·3	22·6±1·1	18·29±0·50
N1 ...	26·5±0·9	25·8±0·8	27·6±1·1	26·3±0·8	25·0±1·3	27·3±1·1	26·42±0·39
N2 ...	21·9±0·9	21·7±0·7	21·3±0·9	21·9±0·8	22·0±1·1	26·1±0·9	22·18±0·36

Tables III to VI summarise in tabular form the results obtained, analysed in their various age-groups, together with their standard errors; while in Table VII, the combined results for all ages are given. In the tables, D represents the duction at distance, N the duction at near, 1 represents a flat target, and 2 a stereoscopic target. All results are expressed in prism dioptres. Table VIII shows those groups where significance, or bordering on significance, has been established.

TABLE V.—*Synoptophore*

ABDUCTION

Mean Values and Standard Errors

Prism Dioptres

Measures	Age 0-20 years	Age 21-30 years	Age 31-40 years	Age 41-50 years	Age 51-60 years	Age 61+ years	All Ages
D1 ...	10·4±0·2	11·0±0·3	11·1±0·3	11·0±0·3	10·5±0·4	10·2±0·4	10·78±0·12
D2 ...	12·2±0·4	11·9±0·4	11·9±0·4	11·6±0·3	11·5±0·4	11·2±0·5	11·77±0·16
N1 ...	12·5±0·3	12·8±0·3	13·5±0·4	12·9±0·3	11·7±0·4	11·5±0·4	12·63±0·13
N2 ...	13·9±0·4	13·3±0·4	13·9±0·4	13·5±0·3	12·7±0·5	12·0±0·5	13·36±0·16

TABLE VI.—*Synoptophore*

ADDUCTION

Mean Values and Standard Errors

Prism Dioptres

Measures	Age 0-20 years	Age 21-30 years	Age 31 40 years	Age 41-50 years	Age 51 60 years	Age 61+ years	All Ages
D1 ...	37·8±1·2	39·3±1·7	40·8±2·2	36·4±1·6	35·8±1·8	40·9±1·7	38·47±0·76
D2 ...	39·3±1·9	42·2±1·9	42 2±2·2	37·0±1·6	39·3±1·9	42·1±1 4	40·33±0·79
N1 ...	51·9±1·4	53 7±1·9	55·4±2·1	47 4±1·9	48·2±2·5	48·9±2·1	51·36±0·83
N2 ...	50·6±1·8	54·3±2·0	55·0±2·5	48·3±1·8	48·9±2·1	51·0±1·9	51·68±0·86

Influence of Age.—From an examination of those rows of Tables III to VI where significance (or bordering on significance) has been established, the following results are obtained:—

Variable Prism Stereoscope:—

Adduction D2. Apart from age group 0-20, the means show a progressive increase as age increases.

Adduction N2. The significance is due mainly to the influence of age group 61+.

Synoptophore:

Abduction N1. The means increase in value up to age group 31-40, followed by a progressive falling-off as age increases.

Abduction N2. The means remain steady up to age group 41-50, and then decline for the remaining two groups.

Adduction D1. A progressive increase to ages 31-40, and then a decrease for the next two groups, followed by a rise for ages 61+.

Adduction N1. A progressive increase to ages 31-40, but the remaining groups are more or less steady at a much lower level.

The above analysis does not appear to show any general law regarding the influence of age on the measurements. When this finding is coupled with the fact that where significance has been established for any one row of tables III to VI for one type of instrument, there is no corresponding significance for the other type, it would appear that, while noting the significance, no particular importance should be attached to it. It is therefore assumed that all ages can be combined, and the mean differences between the two types of target can now be discussed.

Influence of type of target.

Table VII gives the means for all ages, with the two types of target. In order to find whether there was any significant difference between D1 and D2, and between N1 and N2 for abduction and adduction for each of the instruments used, Table IX was drawn up; this gives the results of the analysis.

TABLE VII

Mean Values and Standard Errors, All Ages

Prism Dioptres

	Variable Prism Stereoscope		Synoptophore	
	ABDUCTION	ADDUCTION	ABDUCTION	ADDUCTION
D1	7·97±0·10	17·68±0·26	10·78±0·12	38·47±0·76*
D2	9·09±0·15	18·29±0·50*	11·77±0·16	40·33±0·79
N1	13·61±0·16	26·42±0·39	12·63±0·13*	51·36±0·83*
N2	12·04±0·15	22·18±0·36*	13·36±0·16*	51·68±0·86

*Significance or bordering on significance.

The differences were tested by the use of the formula

$$\text{Standard error of differences} = \sqrt{S_1 + S_2}$$

where S_1 and S_2 are the standard errors of the means of the component parts, as given in tables III to VI.

Where, however, this method did not yield significant differences, the more rigorous method of using individual differences was used; that is to say, if D1 and D2 were to be compared, the difference D1-D2 was calculated for each

individual. The standard errors computed in this way do not thus include variations due to differences in individuals.

TABLE VIII

Differences between Means of any one row of Tables III—VI for different ages

Variable Prism Stereoscope	Synoptophore
ABDUCTION	
D1 No Significant Difference	No significant Difference
D2 No Significant Difference	No significant Difference
N1 No Significant Difference	Significant Difference
N2 No Significant Difference	Significant Difference
ADDUCTION	
D1 No Significant Difference	Bordering on Significance
D2 Significant Difference	No Significant Difference
N1 No Significant Difference	Significant Difference
N2 Significant Difference	No Significant Difference

TABLE IX

The Differences D1-D2 and N1-N2 (all ages)

Prism Dioptres

Variable Prism Stereoscope		Synoptophore	
ABDUCTION		ABDUCTION	
D1 ...	7·97	D1 ...	10·78
D2 ...	9·09	D2 ...	11·77
D1-D2 ...	-1·12*	D1-D2 ...	-0·99*
N1 ...	13·61	N1 ...	12·63
N2 ...	12·04	N2 ...	13·36
N1-N2 ...	+1·57*	N1-N2 ...	-0·67*
ADDUCTION		ADDUCTION	
D1 ...	17·68	D1 ...	38·47
D2 ...	18·29	D2 ...	40·33
D1-D2 ...	-0·61	D1-D2 ...	-1·86
		(bordering on significance)	
N1 ...	26·42	N1 ...	51·36
N2 ...	22·18	N2 ...	51·68
N1-N2 ...	+4·24*	N1-N2 ...	-0·32

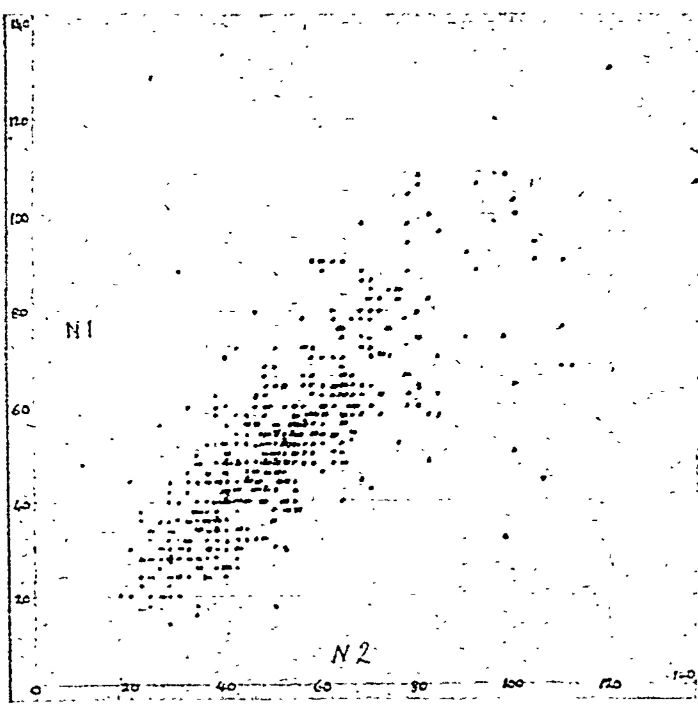
* Significant Difference

Table IX shows that significant difference in the two types of target is present in most but not all of the ductions tested. These differences were not all in the same direction, nor, from the practical point of view, could they be considered as being great.

TABLE X
Regression Co-efficients
a and c where
D1=a D2; N1=c N2; for all ages

	Variable Prism Stereoscope	synoptophore
ABDUCTION		
D1 = a D2	0·81	0·91
N1 = c N2	1·15	0·94
ADDUCTION		
D1 = a D2	0·98	0·97
N1 = a N2	1·20	1·01

TABLE XI
Relationship between N1 and N2
Synoptophore, all ages, adduction
Prism Dioptres



Regression Co-efficients.—Assuming that there was a constant relationship between D1 and D2, and between N1 and N2, the regression co-efficients were calculated for the various age groups, based on the formulae

$$D1 = aD2$$
$$N1 = cN2$$

where a (or c) measures the ratio of D1 to D2 (or of N1 to N2).

Table X gives the results of these calculations, which were found to fit the data very well. Table XI demonstrates one graph constructed to show the relationship between N1 and N2 adduction, for all ages on the synoptophore.

TABLE XII

ALL AGES

Ratio : $\frac{\text{Synoptophore}}{\text{Variable Prism}}$

ABDUCTION	
D1	1·35
D2	1·29
N1	0·93
N2	0·98
ADDUCTION	
D1	2·18
D2	2·21
N1	1·94
N2	2·33

The regression co-efficients are all in the region of 1, and for *practical purposes may be considered as being unity.*

It can therefore be concluded that in the measurement of the horizontal ductions, there is no practical difference in the results obtained in using the two types of target.

Comparison of results on the two instruments.

In order to compare the results obtained on the variable prism stereoscope and the synoptophore, Table XII was drawn up. This shows the ratio Synoptophore : Variable Prism Stereoscope for all ages. In abduction, the ratio varied between 0·93 and 1·35, while in adduction the range was 1·94 to 2·33. One may conclude therefore, *that in abduction similar results are obtained at near* on the two instruments; while at distance the results on the synoptophore will be about one-third higher in value than on the variable prism stereoscope. In adduction the results on the synoptophore will be about double those obtained on the variable prism stereoscope.

SUMMARY

561 subjects were examined on the synoptophore and variable prism stereoscope, and their horizontal ductions were compared from the point of view of age and 2 types of target. The effects of age and of both types of target were found to be slight.

Difference in the results obtained on the two instruments are described and analysed.

The above investigation was carried out with the aid of a grant from the Spencer Research Fund. I have to thank Dr. R. A. Robb, of the Mathematics Department of the University of Glasgow, for the statistical work.

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ADENO-CARCINOMA (MIXED TUMOUR) OF THE LACRIMAL GLAND*

BY

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THE total number of "mixed" tumours of the lacrimal gland hitherto reported appears to be less than three hundred, so any new case is still of importance. The case here described presents certain special features not without interest.

The commonest story is that of a patient complaining of a lump under the outer part of the upper lid, over which the skin is freely moveable. This may or may not be accompanied by exophthalmos, diplopia and loss of vision. Treatment consists of local removal, and in the majority of cases there is no recurrence.

Such tumours sometimes show local malignancy, and may bring about the death of the patient after repeated operation or extenteration of the orbit. A fatal termination may also be due to direct spread, in one case to the meninges and involving the cervical glands (Jack and Verhoeff). Lane found metastasis in seven out

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of ninety-five cases, and Godtfredsen found metastasis in lymphatic glands in three out of ten cases. Mr. Dickson Wright tells me that he knows of five or six cases in which general dissemination, especially involving the liver, has taken place.

Now that the elements suggesting mesodermal origin are explained as arising from the metaplasia of epithelial cells, and that this explanation has been accepted, all the varied nomenclature and varieties based on the presence of mesodermal tissues become inaccurate and outdated. They will, however, continue to serve to stress the degree to which metaplasia is possible.

The tumour removed from the case here recorded has been examined and described by Mr. T. H. C. Benians, and his report is published herewith. He has also supplied some excellent microphotographs, two of which show a mass of tumour cells being squeezed into a cone with blood from a ruptured capillary, and lying free in a gland compartment (Figs. 4 and 5). This, we consider, might provide both explanation and cause of dissemination by the blood stream.

A healthy-looking girl, aged nineteen years, came to my out-patients on September 4, 1946. She was suffering from marked proptosis of the left eye, and she gave a history that this had first been noticed two years ago, but had increased materially during the past four months. The protrusion amounted to about a fifth of an inch. There was no divergence, but, as the photograph suggests, the depression usually found in a proptosed eye, may have been somewhat greater than usual; there was no diplopia, no suggestion of conjunctival or other inflammation or congestion, and, apart from the prominence of the eye and pain for the last two days, the patient had no complaints.

Vision of the right eye was 6/5, and of the left 6/9, and there was no field defect. Vision with the left eye later became subject to fatigue with intermittent blurring. Both eyes were slightly and similarly hypermetropic, but correcting lenses made no difference to the visual acuity. The pupils were equal and active, the media clear, and the only abnormality within the eye was slight left papilloedema without any haemorrhages. Palpation around the globe revealed no resistance, but it seemed evident that a tumour must be present, presumably within the cone of muscles, and a provisional diagnosis of meningioma of the optic nerve was made.

An X-ray picture taken by Dr. Cochrane Shanks to show the optic foramina, indicates no disparity. Other photographs show no sign of the tumour. I referred the case to Mr. Eugene Wolff for his opinion, and he agreed with me in thinking that a meningioma of the optic nerve was the most likely diagnosis. The outward appearances are well shown in the accompanying photographs (Figs. 1, 2, 3).

She was admitted to hospital and I asked Mr. Dickson Wright to see her with a view to operation; it was decided that the orbit should be explored from above, after a left frontal craniotomy.

Mr. Dickson Wright has given me the following description of the operation:

December 12, 1946. "Lt. frontal craniotomy (Mr. Dickson Wright). G.A. (Dr. Cave).

1. Trotter flap—Burrs and Gigli saw. Hinged on temporalis muscle.
2. Orbital roof thinned—removed.
3. Whole supraorbital ridge resected in one piece with Gigli saw and restored to its place after the removal of tumour.
4. Resection of tumour of lacrimal gland which extended backward to apex of orbital cavity. Removed intact with surrounding tissue. Levator palpebrae muscle and possibly its nerve-supply damaged.
5. Closure in layers. Dural hitch sutures to avoid epidural clot. Small temporal drainage tube.

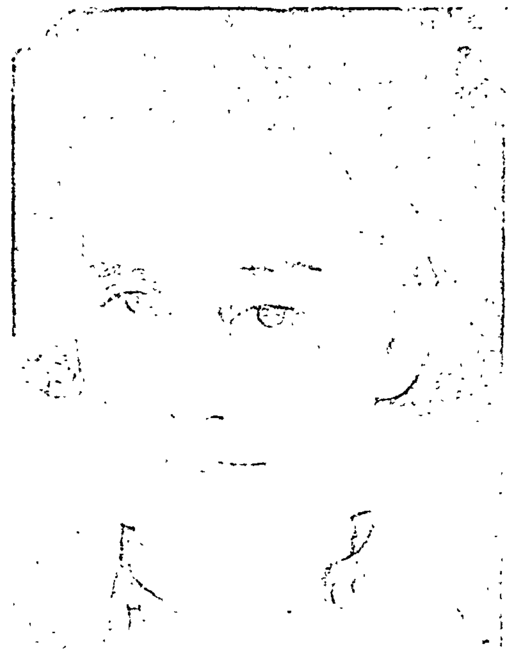

FIG. 1.
Full face.

FIG. 2.
Side view of affected eye.

FIG. 3.

Side view of unaffected eye.

December 21, 1946. *Stitches and tube removed.*"

Mr. Dickson Wright did not see the normal gland separately and considers that a tumour of this size would have obliterated it.

X-ray treatment was carried out by Mr. Anthony Green, who makes the following comments:—

"*In view of the fact that similar tumours in the parotid gland had proved sensitive to irradiation in many instances, it was considered well worth while giving treatment, provided the eye could be adequately screened.*

"A plaster-cast model of the head was made, and a wax mould fitting to the face so that the X-ray beams were carefully directed to the site of the growth. A small protective piece of lead rubber was built in to the wax so that direct irradiation to the globe was avoided as far as possible.

"Tissue dose calculated at the lacrimal gland 4,783r. in 4 weeks.

"The eye was slightly sore after the treatment, but *the reaction cleared up quickly, and the oedema of the eye settled down.*"

Mr. T. H. C. Benians reports as follows:—

A rounded flattened tumour $3\frac{1}{2} \times 1\frac{1}{2}$ cm. with a thin fibrous capsule and irregular bossy surface. It is firm and elastic, showing on section an opaque yellowish-white mottled surface with occasional fibrous strands and apparently very scanty blood-supply, though a few small subcapsular haemorrhages are present. The lacrimal gland was not identified. Without entering into the discussion on origin and nomenclature that has for many years centred on growths of similar type arising mainly in the salivary glands, one can say that the microscopic picture is that of an adenoma with patches of "mucoid" degeneration (Cystic basalioma of Godtfredsen; Pleomorphic adenoma, Willis). Structurally it shows some large

parenchymatous areas in which the cells have either a solid acinar or a cribriform arrangement (Fig. 4), the latter showing few or many pseudotubular or acinar spaces filled with a palely staining eosinophilic hyaline substance. Other areas are composed of small cysts or dilated acini similarly filled. Elsewhere single or grouped tubules lined by radially arranged cells, sometimes in two layers, form separate entities of more normal anatomical type. The tumour-cells are moderately uniform in size and pale, with a round nucleus of relatively large size which shows a well marked chromatin network and one or more nucleoli. Some cells contain small droplets of hyaline material, and a small proportion are of giant size hugely distended with hyaline droplets. The latter are found only in the more anaplastic parts of the growth.

Vascular spaces are abundant in some areas, and mostly contain blood. They lie in the stroma usually close to the gland element, and are formed of a single layer

FIG. 4.

Showing general adenomatous structure of growth with torsion effects (×75).

of fine endothelial cells; a few large, better formed vessels traverse the structure of the gland.

The intimate stroma is of denser bands of collagen than the capsule, and tends to divide the parenchyma up into more or less regular large or small compartments. In the larger masses of cells the collagenous supporting structure is entirely absent. The "mixed" element of the tumour is rather scanty, and consists of irregular patches of hyaline material in which scattered epithelial cells can still be recognised. This material blends with and may ablate both the cellular and collagenous elements of the growth.

The capsule, or more probably false capsule, is thin and made up of collagen fibrils with here and there intercalated compressed tumour-tissue. The part of the gland examined close to the capsule shows in several places the effect of torsion or pressure on the tumour cells, which have assumed a spindle-shape and stain densely. A block of such cells is seen forced into a cone and lying free mixed with blood in an adjacent compartment (Fig. 5).

Sections of the tumour show a remarkable amount of this cell distortion, some of it in small patches deeper in, as though force had been exerted through a band of stroma traversing the region. Tearing of the thin-walled vascular spaces was observed. If these changes occur during operation, dissemination by the blood

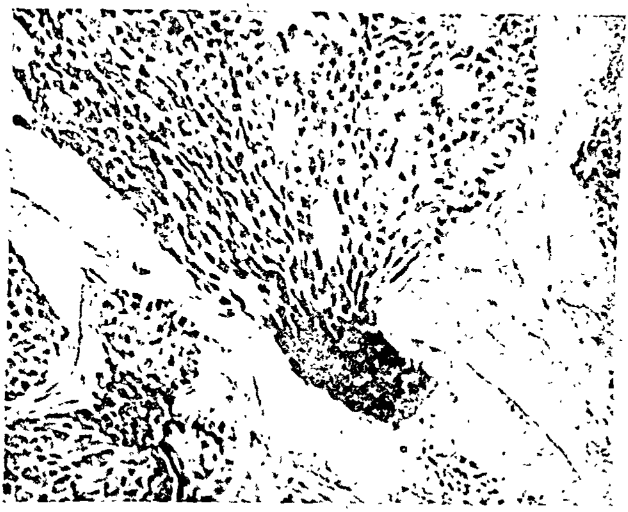

FIG. 5.

Higher power picture of same (×300).

stream would no doubt be possible, and since the growth was removed by free exposure after raising the orbital roof and presumably without undue trauma, it seems that the cells of this tumour may be of a very soft, almost diffluent character.

From the strictly histological standpoint, and judging by the usual criteria, this tumour would appear to be benign, but it is clear from Godtfredsen's paper that growth behaviour in this group is not consistent with microscopical structure, and that these tumours must be regarded as essentially malignant.

In Fuchs' Diseases of the eye, one finds the statement: "New growths of the lacrimal gland are mostly mixed tumours in which the connective tissue of the gland as well as the epithelial portion participates. As indeed the one or the other part predominates in the histological pictures one speaks of fibroma, myxoma, lymphoma, sarcoma or of adenoma, carcinoma or cylindroma."

Morax in his Pathology stresses the slight vascularity and small amount of protoplasm, also the hardness, due to great development of supporting tissue, encapsulation and yellow colour of the tumour.

Seen again in October, 1947, the patient appeared to be in excellent health. Her only complaint was that the left eyebrow, which had been shaved, had failed to grow again. The left eyelid drooped somewhat, but not enough to cover the pupil. She had no diplopia and no pain, and it is interesting to note that she had not suffered from dryness of the eye, even in the hottest weather. The left eye had developed some hypermetropic astigmatism (+2·50 D.S. with +1·75 D.C. Axis 70), but when this was corrected, vision proved to be 6/9 as before operation. The fundus was normal. There was no sign of secondary growths in glands or liver.

I saw her again on May 23, 1949, and found that she had been practically bedridden for six months. She keeps her bed partly because of weakness but chiefly because any form of exertion causes her to be sick. She is very thin.

The left eye is exophthalmic, the lower two-thirds of the cornea being keratinised, vascular and opaque, and the fundus can be seen only dimly through the remaining part. It was possible to make out that the disc was swollen. The orbit is evidently filled with a recurrence which projects forwards above the eye, where it is very hard and tender. The eye has been immobilised for some time past, presumably through involvement of the nerves at the back of the orbit, and during the last month the right eye has been similarly involved, but the optic disc is normal, and there is no evident loss of vision. The lid droops, the pupil is semi-dilated, and the eye cannot be moved in any direction. There is no evidence of any secondary growth, but the abdominal wall was found to be somewhat rigid. Her doctor tells me that she eats very little and it is evident that her weakness is progressive.

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THYROIDECTOMY AND THYROTROPIC EXOPHTHALMOS (EXOPHTHALMIC OPHTHALMOPLEGIA)*

A Review of 1001 Thyroidectomies

BY

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IT has been noted since the early days of thyroid surgery that the exophthalmos of primary thyrotoxicosis (Graves' disease) did not always subside following an otherwise successful thyroidectomy, but that in certain cases it even progressed. Benedict and Knight (1923) of the Mayo Clinic described a case of progressive exophthalmos following thyroidectomy performed six months previously, and there are now many other reports in the literature of this sequence of events. Zimmerman (1929) recorded 11 cases in which this condition followed thyroidectomy, and in Russell Brain's (1944-45) series of 61 cases there were 11 which were post-operative. Mann (1946) in a series of 18 cases observed during the war years, reported 7 post-thyroidectomy cases. Robertson (1945) reported 9 similar cases with the loss of both eyes in two cases and the loss of one eye in two other cases. With similar cases being reported in increasing numbers, it began to appear that thyroidectomy was associated with a definite risk of thyrotropic exophthalmos. Robertson (1945) states that he does not

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think he would operate on a patient over 40 years of age who, in addition to exophthalmos, showed lid oedema.

In this apparent increase in the incidence over the last few years two factors were probably operating. The first was that the condition was now recognised as a clinical entity, distinct from the exophthalmos of primary Graves' disease, and as such, appeared in the literature. The second, and more problematical, was that the increase was due to some other factor such as the emotional stress of the war. In support of this Mann and Russell Brain both found a history of psychic trauma to be common in their cases.

The question then arose as to whether thyroidectomy resulted in the risk of progressive exophthalmos that the above figures seemed to suggest, or whether the striking clinical features of the condition and frequent sequelae of blindness had led ophthalmologists to overstress the danger. It was therefore felt that a large series of patients who had been submitted to thyroidectomy should be reviewed and an attempt made to assess the true frequency of the condition, both in its grosser form and in the milder asymptomatic form.

It was decided to review all the cases of toxic goitre admitted to the Royal Free Hospital under the care of the late Cecil Joll between the years 1940 and 1944 inclusive. These numbered 1,001 and of these 986 cases had been submitted to thyroidectomy. A questionnaire detailing the symptoms and signs of thyrotropic exophthalmos was prepared and sent to the family doctor of those patients who had been operated on. In instances where the patient was known to have moved from the original district or no reply was received from the doctor a questionnaire, necessarily less detailed, was sent to the patient.

Replies were received from 58 per cent. of those to whom the questionnaire was sent. Any statistical analysis is therefore impossible, but at the same time it is thought that the figures are of interest, and perhaps significant.

An analysis of the 1,001 cases reviewed is given herewith in Table I:

TABLE I

(i) Number of female patients who replied ...	487
(ii) Number of male patients who replied ...	46
(iii) Number of patients who died after operation	36
(iv) Number of patients who could not be traced ...	105
(v) Number of patients who did not reply ...	312
(vi) Miscellaneous	15
Total ...	1,001

Referring to Table I above, it is to be noted that 36 patients have died since operation. In 27 of these cases the cause of death was ascertained, and in no case was there any suggestion of thyrotropic exophthalmos before or at the time of death. Pneumonia was a frequent cause of death of those patients who died soon after operation, while later deaths were often due to carcinoma. Excluding the groups (iii), (iv), (v), and (vi), it is found that only 533 cases are left for consideration for the final analysis.

Each case history was then taken and considered in the light of the pre-operative findings and the reply to the questionnaire for evidence suggestive of thyrotropic exophthalmos. As a result of this 49 patients were asked to report to Moorfields Eye Hospital for further detailed investigation. Twenty patients did not report and ultimately 29 patients were examined. Of these, 9 showed no evidence of any disease whatever, and of the remaining 20, 5 patients showed evidence of hyperthyroidism and 8 were slightly or mildly myxoedematous and were controlled by thyroid extract. One patient suffered from post-operative tetany and one was being treated with stilboestrol for pruritis vulvae. Others showed a variety of minor complaints. Only three patients showed slight evidence of thyrotropic exophthalmos and their case histories are summarised below :—

Case 1. Mrs. S. G., aged 24 years, had a partial thyroidectomy for Graves' disease in 1941. When seen at Moorfields in 1947 she was myxoedematous and complained that her eyes were becoming more prominent. Her eyes were proptosed and the lids oedematous. She appeared to be a definite example of post thyroidectomy thyrotropic exophthalmos.

Case 2. Mrs. C. C., aged 58 years, had a partial thyroidectomy for Graves' disease in June, 1941. Subsequently she became myxoedematous and was given thyroid extract, which she later discontinued. When seen at Moorfields in November, 1947, she had the typical features of myxoedema together with chemosis and proptosis. In this case the myxoedema was complicated by excess pituitary thyrotropic hormone.

Case 3. Mrs. A. B., aged 39 years, became mildly myxoedematous following a partial thyroidectomy in 1944. On examination at Moorfields in addition to slight exophthalmos she showed some puffiness of the upper lids. She appeared to be a mild case of myxoedema with some excess thyrotropic hormone.

The diagnosis of thyrotropic exophthalmos is suggested by the presence of exophthalmos, swelling of the lid due to increasing fat and later stasis oedema, oedema of the conjunctiva and orbital contents and weakness of the extra-ocular muscles. The greatest difficulty in diagnosing mild cases is that there is no readily available means of assessing the thyrotropic hormone content of the blood, and biopsy of the orbital contents is usually not feasible. Therefore the diagnosis and the differential diagnosis of thyrotropic exophthalmos must be purely clinical. However, these cases showed definite evidence of mild thyrotropic exophthalmos, and slight myxoedema. The exophthalmos was slight and none

showed any evidence of diplopia or other disturbance of ocular function. *In no case was there any evidence of venous congestion* of the retinal vessels or oedema of the disc, nor any gross oedema of the eyelids, nor gross chemosis.

The ages of the patients were evenly spread from late youth to early old age whereas thyrotropic exophthalmos is largely a disease of late middle life. Further, they were all females and the condition is known to be 36 times more common in males than females (Mann, 1948). All three had had seven-eighths of the thyroid removed.

DISCUSSION

The most surprising feature made evident by this investigation is the infrequency of thyrotropic exophthalmos as a sequel to thyroidectomy. The figures of Mann (1946), and others quoted above had suggested that the incidence would be certainly appreciable. It was therefore expected that the review of such a relatively large number of cases in which thyroidectomy had been performed would have revealed a few gross cases and several minor cases of thyrotropic exophthalmos. Gross cases of the condition, owing to their striking clinical features, would obviously have required hospitalisation and would be unlikely to have escaped notice. Nothing suggestive of this type of case was found in the replies received either from the patients themselves, their family doctor or in the notes on the cause of death of patients who had died since operation. Since in all, only three mild cases were discovered the incidence after thyroidectomy appears to be only a fraction of one per cent. Part of this incidence must be attributed to the care in the selection of cases for operation and the technical skill of a surgeon of great experience, the late Cecil Joll. These findings are confirmed in a personal communication from Sir Thomas Dunhill. In his experience of thyroidectomy extending over forty years he has only encountered two cases of thyrotropic exophthalmos. Each of these had been operated on by another surgeon. Among his own operation cases there were several in which some of the signs were those encountered in exophthalmic ophthalmoplegia and in which tarsorrhaphy was performed because of the extreme exophthalmos with chemosis and ulceration, but in all of these the eyes became normal, except in one patient. In this patient one eye was lost—the other eye became normal. Photographs of each of these patients have been published. (Dunhill, 1930.)

With careful surgery it seems that the risk of post-operative thyrotropic exophthalmos is more apparent than real.

SUMMARY

1. Recent literature suggests that thyrotropic exophthalmos commonly follows thyroidectomy.
2. To investigate the true incidence of this as a complication, a questionnaire was submitted in regard to 1,001 patients admitted to the Royal Free Hospital for thyroidectomy from 1940-1944.
3. Satisfactory information was obtained in 584 cases.
4. Three cases, only, of thyrotropic exophthalmos of a mild degree were found.
5. No gross cases of the condition occurred.
6. The condition is rare as sequel to thyroidectomy.

This study was undertaken at the suggestion of Miss Ida Mann and I am much indebted to her for her help and guidance. I wish also to thank Dr. Elizabeth Everitt, formerly of the Royal Free Hospital, for her abstracts of case histories, and Miss Saunders for help with the clerical aspects. Acknowledgments are also due to the Medical Committee of the Royal Free Hospital for their permission to use the notes of the late Mr. Cecil Joll The secretarial expenses for this investigation have been met by Moorfields Eye Hospital, who made the necessary allocation of funds from the Royal London Ophthalmic Hospital Research Fund.

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THE GLASS ROD TEST IN GLAUCOMATOUS EYES*

BY

T. L. THOMASSEN

(From The Institute of Ophthalmology, London, Director of Research, Sir Stewart Duke-Elder)

IN his first paper on the aqueous veins Ascher described the so-called "glass rod phenomenon"[1]. This phenomenon is produced by compressing the recipient vessel just beyond the meeting-point of an aqueous vein and a blood vein. There are two possible results. The aqueous may push away and replace the blood in the recipient vein so that it enters the vein previously filled with

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blood. This is called a *positive glass rod test* or *aqueous influx phenomenon*. Alternatively, blood may flow backwards into the aqueous vein, filling it wholly or in part. This is called a *negative glass rod test* or *blood influx phenomenon*.

In normal eyes Ascher has shown[1, 2] that this test can be positive or negative in different aqueous veins. According to his law of constancy[4], however, the test will always give the same result, positive or negative, when performed on the same aqueous vein even after an interval of years. If more than one aqueous vein is present in the same eye, one may show a positive and the other a negative glass rod test. He has also found that aqueous veins situated on the temporal side of the globe show a positive test more often than those on the nasal side. In his first paper on this subject ([1] p. 32 and [2] p. 1192) Ascher says that the ratio of aqueous veins with a positive glass rod test to those with a negative test is about seven to five. In a later paper ([4] p. 1084) he has found statistically that the glass rod test is positive only in two-fifths of all eyes with aqueous veins.

In eyes suffering from simple glaucoma Ascher has made the remarkable finding[1, 2, 3] that the glass rod test is invariably negative except when the pressure is controlled by either miotics or surgery. Goldmann[8] has confirmed this and so does de Vries[12]. The latter has, however, found that the test can be positive even if the ocular pressure is increased, provided the intra-ocular pressure is in the decreasing phase.

Clinical Investigations.

Twenty-four patients with 35 eyes suffering from simple glaucoma and with an aqueous vein suitable for the glass rod test were examined. The glass rod test was applied to each of these eyes many times. Observations were usually made half-hourly through a large part of the day and in most cases for more than one day, sometimes up to five. As the ocular tension was expected to influence the result of the test, the tension was measured with a Schiötz X-tonometer after each test. Before tonometry a drop of 1 per cent. pantocaine was instilled into the eye. The drops and the manipulations irritated the eye and produced a state of hyperæmia which usually disappeared in half an hour. If the hyperæmia persisted, a further delay in testing was necessary. The eyes examined had not been operated on, and usually not treated with miotics for 24 hours. The tension in most of the eyes oscillated considerably during the period of observation and it could be seen that the result of the test varied with the height of the ocular tension and with the phase of its oscillations.

When the bulbar tension was in an increasing phase the test was never positive. It is, however, often difficult or even impossible to judge the result of the test in this phase as the aqueous veins are usually filled spontaneously with blood. When the bulbar tension was in a decreasing phase de Vries' findings were confirmed in so far as the test was sometimes found to be positive even when the bulbar tension was increased. It was, however, by no means invariably so. In this connection it does not seem to matter whether the decreasing phase is spontaneous or produced by pilocarpine. When the tension remained on a steady but increased level the test was usually negative. In a few cases, however, it was positive in spite of a tension up to 45 mm. Hg.

Ascher's finding that the glass rod test is always negative in glaucomatous eyes when the bulbar tension is increased was thus not confirmed here. The test is definitely more often negative in glaucomatous eyes. Nor was Ascher's law of constancy found to apply to glaucomatous eyes. Repeated examinations of the same aqueous vein very often gave different results. In 21 of the glaucomatous eyes examined, an inconstancy of the glass rod test was found. In one case for instance the glass rod test was applied to the same aqueous vein 14 times, 9 of which were positive and 5 negative. The bulbar tension oscillated between 15 and 25 mm. Hg during the three days' observation. In this case no direct relationship between the height of the tension and the results of the tests could be observed, although it is probable that the phases in the oscillations of tension determined the variations. The bulbar tension went up and down so quickly that it was impossible to be sure whether the test was carried out during an increasing or decreasing phase.

DISCUSSION.

Some hydrodynamic principles of the aqueous veins will first be explained.

According to Theobald[9] there are 20 to 30 outlets from the canal of Schlemm. Most of them join the veins within the sclera, but one or a few may appear on the bulbar surface before they join a blood vein; the latter are known as aqueous veins. The total amount of fluid emptied through all the outlets in a normal eye must be just as much as is necessary to keep the production and escape of aqueous humour in equilibrium. The outlets, however, differ in size, length and course. Both the amount of fluid which has to be emptied through each of them and their pressures at the point where they join the blood vein must therefore vary from one outlet to another. On the other hand, the pressure in the blood

veins is not uniform. Inside the globe the venous pressure is high but it starts decreasing as soon as the vein enters the sclera. The pressure in the vein just at the meeting point with an aqueous outlet vein may therefore vary considerably.

From this, it is clear that the amount of fluid which normally passes through an aqueous vein, will be specific for each individual vein. Both the aqueous vein and the blood vein will discharge their contents into the recipient vein even if their pressures, within certain limits, are unequal. The ratio between the amount of outflow from the two vessels will depend, among other things, on the ratio between their end-pressures. Some aqueous veins will therefore normally have a higher pressure and others a lower pressure than that of the joining blood vein.

When the recipient vein is compressed the flow through the vessels will be stopped for a while and that vessel which now has the higher pressure will push its contents up into the vessel with the lower pressure. If, for instance the pressure in the aqueous vein is the higher, the glass rod test will be positive. In accordance with hydrodynamic laws, however, the pressure in both vessels will change until the pressure at the first branching higher up the stream is attained. In other words, the final new pressures not only depend on the previous pressures at the meeting point but also on the fall of pressure which takes place in the respective vessels from the most proximal branching. Now, this fall of pressure will be different for each aqueous vein and blood vein and will depend among other things on the distance from the proximal branching to the meeting point. This new local factor is thus of importance in determining the result of the test.

These facts readily explain Ascher's findings as to the glass rod test in normal eyes. The local circumstances are indeed so different for each aqueous vein that the test applied to some veins will be positive, and to other veins negative. It also explains his law of constancy.

The findings in glaucomatous eyes are, however, not so easy to understand. Both Goldmann and Ascher have tried to explain why the glass rod test is negative when the bulbar pressure is increased. Goldmann emphasises [8] that it is due to an increased resistance in the permeable membrane between the anterior chamber and Schlemm's canal. This should result in a low pressure in Schlemm's canal and in its outlets, including the aqueous veins; on the other hand it could cause the increased bulbar tension. If, however, the rate of production of aqueous humour is unchanged, the bulbar pressure and therefore the pressure in the aqueous veins will rise until the outflow is the same as before. A constant decreased pressure in the aqueous veins is therefore only

possible if the production of aqueous humour decreases when the bulbar pressure increases. This may or may not be so, but Bárány's findings [7] seem to indicate that production of aqueous humour is independent of the bulbar pressure.

If Goldmann's conception is correct, the following three facts would suggest that the resistance in the permeable membrane alters very often and quickly and at times is even less than normal.

1. The occurrence of large oscillations in the bulbar tension which usually take place in glaucomatous eyes.
2. The extraordinarily great outflow of clear liquid seen when the bulbar pressure is in a decreasing phase [11].
3. The fact that the glass rod test does not show the same constancy as in normal eyes.

It follows then, that Goldmann's theory can only be accepted if a rapid alteration in the resistance of the permeable membrane can take place and if the production of aqueous humour decreases when the ocular pressure increases. The first of these conditions is improbable and the second doubtful.

Ascher has also explained the negative glass rod test by postulating a decreased pressure in the aqueous veins[4, 5, 6]. He finds it more likely, however, that the hampering of the outflow is caused by a narrowing of the outlets from Schlemm's canal. It is perhaps more credible that such a narrowing may be reversible but Ascher's explanation, like Goldmann's, is entirely dependent on a decreased production of aqueous humour when the bulbar pressure is increased.

The aqueous veins are usually, as Goldmann emphasises[8] direct branches from Schlemm's canal. This is, however, not always the case. When they are direct branches it is impossible that their constriction can cause a negative glass rod test. Such a narrowing would cause an unusually high pressure in the canal of Schlemm and as the glass rod test depends on the pressure at the first branching higher up the stream, the test would tend to be more positive than ever.

In my opinion the cause of the phenomena appearing in glaucomatous eyes must be sought not in the aqueous veins, but in the blood veins. Ascher has also mentioned this possibility [3] but he has not followed it up.

There are two circumstances concerning the venous pressure that will play a part in the determination of the direction of flow. The higher the bulbar pressure, the higher must be the intrabulbar venous pressure. On the other hand, the general venous pressure in the orbit will be the same. The pressure gradient in the veins when they pass through the sclera and along the epi-

sclera must therefore be steeper if the bulbar pressure is high. The fall of pressure from the proximal branching to the point of meeting with an aqueous vein must therefore also be greater, thus tending to cause a negative glass rod test. On the other hand, it has been shown[10] that the venous pressure is high in proportion to the bulbar pressure when the latter is in an increasing phase. This fact also tends to cause a negative glass rod test. When the bulbar pressure is in a decreasing phase, however, the venous pressure is low compared with the bulbar pressure and thus tends to make the test positive. The combination of these facts can explain the irregular findings with the glass rod test in glaucomatous eyes. One has, however, also to take into account the fact that the result of the test is normally vigorous in some veins while in others it is feeble. The fact that it must be easier to change a feeble test than a vigorous one probably explains why the test is sometimes positive even when the bulbar tension is increased and why, in other eyes, the result of the test frequently changes in response to minor oscillation in the tension.

SUMMARY

The glass rod test was applied to 35 eyes suffering from simple glaucoma.

When the bulbar tension was increased the test was usually found to be negative. It was, however, found to be positive when the ocular tension was in a decreasing phase and sometimes when it was on a steady, but increased level. The most striking difference between normal and glaucomatous eyes is that Ascher's law of constancy does not apply to glaucomatous eyes. Early investigators' explanations as to the cause of the negative glass rod test in glaucomatous eyes are discussed. The author emphasises that the state of the venous pressure provides the most rational explanation of the findings.

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EXTRACTION OF CATARACT IN A CASE OF SYMPATHETIC OPHTHALMIA*

BY

F. W. G. SMITH

MARGATE

THE summary in Ophthalmic Literature of an article by A. Franceschetti[1] has prompted me to report this case.

In October, 1946, Mrs. A., aged 79 years, with bilateral cataracts, underwent a left extra-capsular extraction without any obvious operative complications, but two days after operation an acute iridocyclitis developed. The usual treatment was undertaken, and both eyes observed carefully with the slit-lamp. Enucleation was advised after five weeks, as the left eye had a marked flare, many plastic keratic precipitates and new vessels in the iris. The tension was low, and she had recurrent attacks of ciliary pain.

The day after the left eye was enucleated typical sympathetic ophthalmia developed in the right eye, which, after much treatment and many distressing symptoms, settled down, but showed a slight flare, many K.P., posterior synechiae, and the pupil occluded by exudate. The tension became low. By mistake a section of the enucleated eye was not carried out, but clinically all the signs of sympathetic ophthalmia were present. The case had been examined several times with the slit-lamp before operation, and there had been no evidence of previous iritis.

As the projection of light was good in the remaining eye it was felt that some risk might be taken owing to the age of the patient. Nineteen months after the onset of the disease, extraction was undertaken with the usual akinesia, retrobulbar anaesthesia, bridle suture and, in this case, a Stallard's corneal suture. A large corneal section was made, and retraction of the cornea by the suture allowed the excision of a large portion of iris and capsule with a capsule forceps. The lens was lifted out, without vitreous loss, by two Ziegler needles inserted into its substance. 20,000 units of white penicillin in 1 c.c. *aq. dest.* were dropped on the eye before, during and after operation. The removal of the lens was easier than in the case described by J. Herbert Fisher,[2] where the cataract was extracted seven years after the onset of the disease.

The eye settled down quickly, and one month later an opening was made with a fine Graefe knife in the thick but soft membrane remaining. The corrected vision was reduced to 3/60 on account of a white plaque in the macular area, which might have been the result of a coalescence of Dalen's spots, but the peripheral field was full, and the patient was able to get about and undertake household work.

I have found the above method of extraction useful in complicated cataract with many iris adhesions. One Ziegler needle with slight external pressure on the lower pole, or two needles without external pressure, can be helpful in extracting the lens, and also when the capsule has burst in an intra-capsular extraction. A fine straight, non-toothed iris forceps instead of a corneal suture retracts the cornea. I have ceased to use the latter in routine cataract extractions.

The fixation forceps in the illustration are a type used by Dr. Frank Burch (Senior) of St. Paul, Minnesota, and they have many practical advantages. Their 20 into 19 teeth provide excellent fixation, whether the conjunctiva is normal, friable or oedematous,

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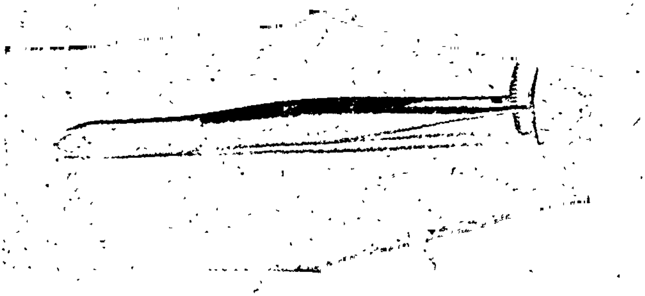

Conjunctival Fixation Forceps.

and the breadth of grip helps to prevent rotation of the eyeball in a Graefe section if the knife is not quite perfect.

It is suggested that, where cataract has developed in cases of sympathetic ophthalmia, fairly early operation might be undertaken when the slit-lamp does not show undue inflammation and the acute recurrences have subsided, despite the presence of keratic precipitates and a slight flare. The irido-capsular membrane may be softer and an opening made more easily to lift out the lens. The same would seem to apply to the after-cataract.

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SIMPLE CAMERA SUPPORT FOR THE OPERATING THEATRE

BY

GY. P. HALBERG, M.D.

ARGENTINA

THE usual photographic tripods are often inconvenient and cumbe[r]some when used in the theatre for the photography of eye operation[s]. For this reason a simple *unipod support* has recently been designe[d]. A short illustrated specification is given below.

The unipod consists of a vertical iron rod, and a horizontal fla[t] iron tongue, supported at 90° by a simple diagonal bar. Th[e] vertical member is ½ in. solid rod, 36 in. in length. The horizonta[l] portion is flat; 24 in. long, 1¼ in. wide and ¼ in. thick. Two slot

10 in. × $\frac{3}{4}$ in. are made in its long axis to facilitate the adjustable fixing of a ball and socket camera support (Fig. 1).

The whole assembly is fixed to the operating table as shewn in Fig. 2.

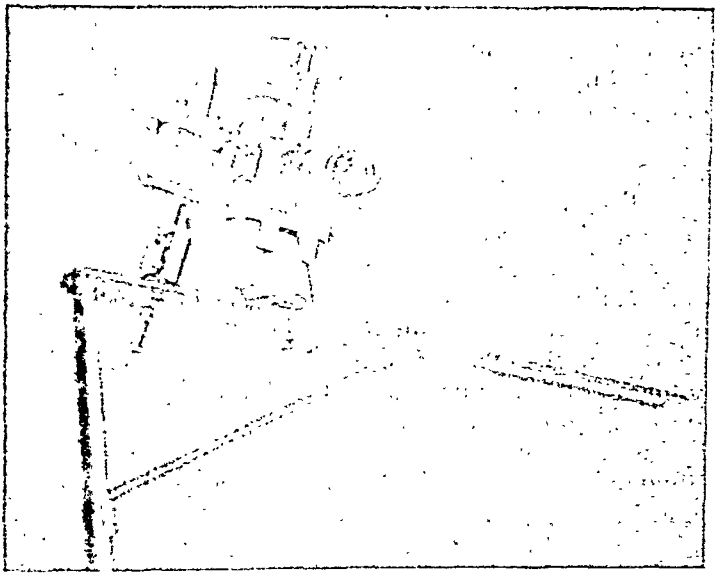

FIG 1

Unipod camera support, with camera and "ball and socket joint."

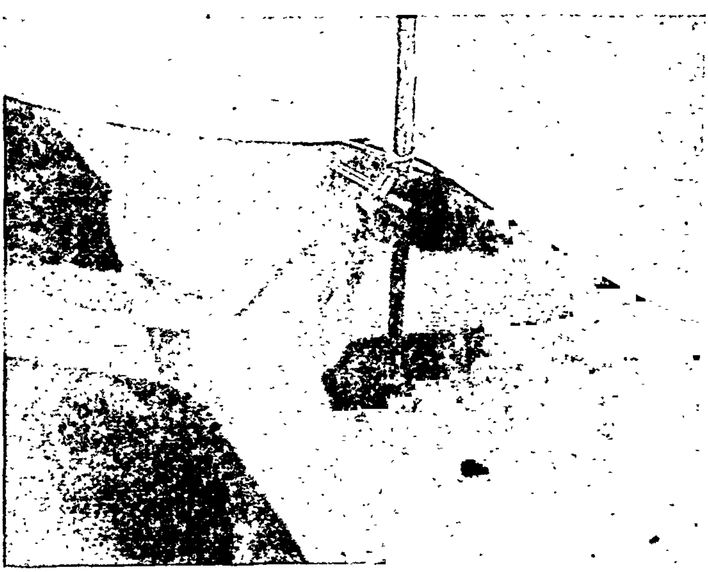

FIG. 2.

Picture shows how unipod support is fixed to the operating table.

OPHTHALMOLOGY IN AUSTRALIA

THE Ninth Annual Congress of the Ophthalmological Society of Australia (B.M.A.) was held at B.M.A. Hall in Melbourne from October 3 to 7 under the presidency of Dr. Arthur Joyce. Abstracts of the papers will in due course appear in Ophthalmic Literature, but meanwhile the organisers of the Congress are to be congratulated upon their achievement. Dr. A. L. Lance (Sydney), the Honorary Secretary of the Society, had collaborated so efficiently with the local Honorary Secretaries of the Congress, Dr. Esmé Anderson and Dr. S. R. Gerstman of Melbourne, that all the arrangements worked smoothly, and success was finally clinched by the atmosphere of free, informal discussion communicated by the President.

At the opening session members were gratified to hear a message of greeting from Sir John Parsons, a confirmed admirer of Australian scientific talent. Among the contributors to the scientific programme were Dr. Ronald Lowe (Melbourne) and Dr. Hugh Ryan (Melbourne), whose energetic work at the Institute of Ophthalmology and elsewhere in London is fresh in the memory of English ophthalmologists. Another junior ophthalmologist, Dr. K. B. Redmond (Orange), gave a carefully prepared paper on the causation and prevention of blindness. Dr. Kevin O'Day's (Melbourne) discourse on iris tumours was illustrated by excellent microphotographs, and Dr. J. Ringland Anderson (Melbourne) was as stimulating as ever. There were also interesting communications from Dr. J. Bruce Hamilton (Hobart), Dr. Norman Macindoe (Sydney), Dr. G. A. Brew (Melbourne), Dr. J. L. R. Carter (Launceston) and Dr. D. T. Shortridge (Warrawee).

Miss Ida Mann spoke about the movement of macrophages in corneal grafts. She also gave an illustrated account of the Institute of Ophthalmology in London, and showed a film recording her former visit to Australia. A paper in which Mr. Frank Law, President of the Faculty of Ophthalmologists, had recorded his unofficial impressions about ophthalmology under the National Health Service was read out by Mr. J. H. Doggart. Mr. Doggart and Mr. T. Keith Lyle each gave two other talks. One of the afternoons was devoted to a clinical meeting at the Eye and Ear Hospital, where a rich array of material had been assembled. Discussion of the cases followed under the chairmanship of Dr. Walter Gibson (Brisbane). Honorary membership of the Society was conferred upon Mr. J. H. Doggart and Mr. T. Keith Lyle, who expressed to the President their warm appreciation of this honour. It will be recalled that Miss Ida Mann was similarly honoured on the occasion of her previous visit to Australia.

The present writer retains vivid memories of hospitality generously

dispensed by the President and Mrs. Arthur Joyce, Dr. and Mrs. J. Ringland Anderson, Dr. and Mrs. W. Fox, Dr. and Mrs. Kevin O'Day, Dr. and Mrs. Mark Gardner, Dr. Lame Anderson and many others, including the Council of the Australasian College of Surgeons. He will never forget also the expedition to Warrandyte, where Dr. and Mrs. Edward Gault entertained a number of congressists shepherded by his daughter and colleague, Dr. Adelaide Gault. Although Dr. Edward Gault is well into the ninth decade of life, he stood up as straight as a lance, to make his speech at the Annual Dinner. It was at this same banquet that Dr. Archie Anderson (Melbourne) made his memorable *mot*: "Ida came out to us ten years ago, every inch a Mann; and now she's come back a regular Gye."

A medical man who spent several years in Australia described its people as the most hospitable in the world. Certainly nothing could have been kinder than the welcome accorded to the guest speakers from England. Nothing was left undone to promote their enjoyment and to put them at ease in this glorious city, and so the memory of their visit to Melbourne is exceedingly precious—and all the more so, by reason of the enthusiasm with which the coming generation is attacking ophthalmological problems on the continent of Australia.

TASMANIA

On October 12 a meeting of the Tasmanian Section of the Ophthalmological Society of Australia was held at the Royal Society's room in the Tasmanian museum at Hobart. Mr. J. H. Doggart spoke on retinopathy in the diabetic, and Mr. T. Keith Lyle's subject was traumatic surgery of the face. The chair was occupied by Dr. J. Bruce Hamilton, to whom these visitors are deeply indebted for a multitude of reasons. Not only were they hospitably entertained in the home of Dr. and Mrs. Bruce Hamilton, but they were also shown the apple-blossom of the Huon riverside and introduced to a multitude of other delightful friends, including Dr. and Mrs. Alec Budge, who met them on arrival at Wynyard and made them so welcome at Devonport. Dr. and Mrs. Tim Palfreyman were also in the vanguard of those who loaded us with kindness, and other delightful hosts were Dr. and Mrs. J. L. R. Carter, Dr. and Mrs. D. H. Waterworth, Dr. T. G. H. Hogg (a nephew of Mr. Rupert Scott) and Dr. J. L. Grove. Hobart and Launceston seem to be full of warm-hearted people, and Tasmania might well be described as a series of enchanting landscapes.

NEW ZEALAND

The Annual Congress of the Ophthalmological Society of New Zealand took place last May, but a special conference, to which the visiting speakers at the Australian Congress were invited, was held

at Christchurch on October 26 and 27. Miss Ida Mann was unable to attend, though she hopes to re-visit New Zealand in the near future. The President of this gathering was Dr. W. H. Simpson (Wellington), a former Moorfields House Surgeon, whose son, now settled in Vancouver, recently occupied the same post. Dr. Simpson is remarkable for his lively wit and geniality of presence, so that the success of the meeting was virtually certain from the outset. Dr. W. J. Hope-Robertson (Wellington), the Honorary Secretary-Treasurer of this young and vigorous Society, is to be congratulated upon his organising zeal, and great credit is also due to Dr. Harry Wales, the local Honorary Secretary, and to Dr. Lindsay Burns, also of Christchurch. The wives of these four ophthalmologists all played a prominent part in the social side of the meeting.

Mr. J. H. Doggart and Mr. T. Keith Lyle each contributed three papers, and an interesting group of clinical cases was discussed under the chairmanship of Dr. Lindsay Burns, a former Moorfields House Surgeon. A fascinating talk on artificial eyes in ancient Egypt was given by Dr. Rowland Wilson, whose distinguished work at the Giza Memorial Laboratory is known throughout the world of ophthalmology. The width of Dr. Wilson's clinical and scientific interest is remarkable, so that he is able to make stimulating queries and fruitful suggestions about almost every conceivable subject. Certainly he exerted a strong fertilising influence during the discussions which followed the papers.

Before the Christchurch meetings, Mr. Doggart and Mr. Lyle were entertained by the Auckland ophthalmologists at a dinner over which Dr. W. A. Fairclough presided. Dr. H. V. Coverdale, Dr. Graeme Talbot, Dr. Calvin Ring and a number of other old friends were present at what proved to be a most successful evening's entertainment. Here and elsewhere in New Zealand it was a special joy to see former colleagues and house surgeons happily settled, and carrying on with the excellent work which we had learned to expect from them by reason of their former activities in Great Britain. Mr. Lyle snatched a few days away from the preparation of his discourses, and took Mrs. Lyle to browse on the beaches of North Island, and to career over the roads in a car lent by his former house surgeon, Dr. Charles Swanston. Mr. Doggart was generously welcomed at Dunedin by Sir Charles Hercus, the Dean of the Medical School of Otago University, and gave a talk to the students. He was hospitably entertained by Dr. and Mrs. Rowland Wilson, and was also enabled by Dr. Wilson to see something of the work of that enterprising cranio-surgeon, Dr. Murray Falconer. Mr. Doggart also visited Dr. Ryburn at Knox House, under the wing of Dr. John Stewart, and afterwards the latter's father, Dr. Garfield Stewart (Auckland), conducted Mr. Doggart to Queenstown, where

he watched the sun rise over Lake Wakatipu, and revelled in the splendour of Milford Sound. Dr. and Mrs. John Doctor regaled the visitors at their charming Waikanae home, and Mrs. Garfield Stewart once again proved herself to be a wonderful hostess in Auckland.

New Zealand is a land of infinite variety, and it is curious to think how few miles intervene between the austere peaks of the Southern Alps, and the lambs that frolic over the Canterbury plains. Christchurch, whose winding river and green grass recall the quietude of Cambridge and Salisbury, conveys an atmosphere altogether different from that of Dunedin, Wellington and Auckland, but one feature is common to all the cities of New Zealand—a kindly welcome to friends from across the sea.

ADELAIDE AND SYDNEY

Miss Mann and her husband, Professor W. E. Gye, called at Adelaide during their sea voyage to Melbourne, and were welcomed by Dr. and Mrs. A. L. Tostevin, who also lavished hospitality on Mr. Doggart before the Melbourne conference. Mr. Doggart visited the Adelaide Children's Hospital under the guidance of Dr. Geoffrey Barham Black and Dr. D. O. Crompton. On October 14 a number of interesting cases were discussed at a clinical meeting preceded by a dinner to which Dr. Tostevin had bidden his Adelaide colleagues and his visitor. To the writer of this article it was a memorable experience to bestride the Oval cricket ground, to sail across the inner harbour, and to hear the twanging of innumerable frogs intermingled with the kookaburra bird's chatter. The inhabitants of Adelaide have good reason to revere the memory of Colonel Light, whose forethought and determination are mirrored in the lay-out of this lovely city.

Mr. and Mrs. T. Keith Lyle, who travelled *via* Vancouver, reached Sydney on September 25 and were followed two days later by Mr. J. H. Doggart. They spent a few days there before the Melbourne meetings, another day or two before going to New Zealand, and again nearly a week before the final departure on November 4. With Dr. V. M. Coppleson in the chair, the New South Wales representatives of the Royal Australasian College of Surgeons generously entertained Mr. Doggart and Mr. Lyle to dinner at the Australian Club on October 31, and afterwards the visitors each contributed a paper in the lecture hall of the College of Physicians. Dr. Stephen Lynch, who formerly worked at King's College Hospital with Mr. H. Willoughby Lyle, crowned the evening with a rousing welcome by Mrs. Lynch and himself at their beautiful Vaucluse home.

Mr. Lyle also addressed the New South Wales Ophthalmological

Society on November 2—a meeting which Mr. Doggart was unable to attend, because he was basking in the hospitality of Dr. and Mrs. Clifford Colvin at Orange. One of Mr. Doggart's most stimulating experiences was a visit to Dr. Mervyn Archdall at the editorial headquarters of the Medical Journal of Australia. It is seldom realised in England that Printing House, Seamer Street, not only produces that magnificent Journal, but also issues an abundant jet of other periodicals, text-books, works of reference, etc. It was a great privilege to meet the manager, Mr. Noldt, and many other members of Dr. Archdall's happy team of colleagues. This beloved editor was one of the most popular figures at the Melbourne congress, and he was also a guest at Dr. and Mrs. Bruce Hamilton's Hobart party on October 13. The evening which Mr. Doggart spent with Dr. and Mrs. Archdall at their home on November 3 stands out as a treasured memory.

It was a joy to renew friendships with Dr. E. A. Brearley, Dr. W. M. C. MacDonald and Dr. Norman McA. Gregg. Dr. Gregg returned from his world trip shortly after the Melbourne meetings, leaving his wife and family for a further stay in England. It will be recalled that he was a particularly welcome overseas visitor at the B.M.A. Harrogate Meeting this summer. Dr. and Mrs. Darcy Williams were the very personification of kindness, and the writer is for ever indebted to them for bountiful help and attention. Both Mr. Doggart and Mr. Lyle found time to visit the building of the Medical Eye Service, where consultations at reduced fee are available on the clinic system. Dr. Darcy Williams' enterprise was largely responsible for the inauguration of this venture, which has proved a great boon to patients of moderate means.

Other friends to whose kindly welcome and generous hospitality in this thrilling city the writer would like to pay tribute are Dr. and Mrs. Cedric Cohen, who may rest assured of a warm welcome at the forthcoming International Congress, the Honourable and Mrs. Arthur Colvin, Dr. and Mrs. Clifford Colvin, Dr. and Mrs. Arnold Lance, Mrs. Claffy and her son Frank (a former house surgeon at the Central London Ophthalmic Hospital), and Father Frank Flynn, who loomed up in the dawn at Port Darwin with the same endearing smile as of old.

For every name that has been mentioned there are several times as many who contributed to the warmth of our welcome. Every invitation accepted was only one of a number, which the swift passage of time rendered impossible of acceptance. Therefore many hospitable people worthy of mention must perforce be omitted, but they may rest assured that their generosity did not pass unnoticed. We who have been privileged to work as colleagues in peace and in war with men who came from all parts of Australasia felt certain that it would be a joy to enter their homes, and a

source of stimulation to take a share in their professional conferences: but the event exceeded all expectations, so that we are profoundly indebted to the good folk of Australia, Tasmania and New Zealand; and we are fortified in the conviction that we should mingle more closely with each other. Let fresh links be forged, and that right early.

BOOK NOTICE

Ophthalmic Medicine. By JAMES HAMILTON DOGGART. Twenty-eight coloured plates, 87 text figures. J. and A. Churchill, Ltd. 1949. Price, 32/-.

Only a select few in this country have attempted the difficult task of writing a text-book on the medical aspects of ophthalmology. In the wake of the late Sir William Gowers and Foster Moore comes J. H. Doggart with this admirable book on "Ophthalmic Medicine" succeeding by 24 years Foster Moore's second edition of Medical Ophthalmology, published in 1925. The qualities necessary to do full justice to this subject are considerable. The author of "Ophthalmic Medicine" has brought to this work the stored riches of his extensive clinical experience, a wide knowledge of his specialty and of its many contacts with the main body of medicine, the application of his philosophic mind to controversial matters, and an ease of expression in good English which makes the reader enjoy the book as an absorbing narrative. It is touched and enlightened here and there with advice which shows clearly the author's insight into the art, apart from the technique, of practising medicine. The book has achieved the author's purpose in its presentation of a comprehensive survey of the disorders and diseases of the eye in association with pathological changes in its adjacent structures and in remote parts of the body. In this work he has correlated recent discoveries with the traditional aspects of medical ophthalmology.

The physician will be much helped by four well-written chapters on the history of a case, symptoms, methods of examination and physical signs, and the ophthalmologist by the admirable dissertations on allergy; vitamin defects; inflammatory syndromes; focal, virus and fungus infections; metabolic disorders; and disturbances in endocrine function among other topics of general medical interest.

This book is a praiseworthy attempt to compress into 300 pages all that is sound in the teaching of ophthalmic medicine. It is well illustrated, and a fair bibliography is given at the end of every chapter. There is little to criticise adversely. It is evident that a mistake has been made in Plate XX, Fig. 2, where a tigroid

fundus is printed instead of that of an albino. Plate I, Figs. 1 and 2 could be more artistically executed, and this also applies to the drawings of a pterygium and a dermolipoma of the bulbar conjunctiva.

The book is well produced, and will be valued by physicians and ophthalmologists as a sound contribution to matters concerning both.

NOTES

Death

As we go to press we learn with deep regret of the death of Sir Herbert Lightfoot Eason, C.B., C.M.G., President of the General Medical Council. An Obituary Notice will be published in the next number of the Journal.

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Honours

At their meeting in Chicago in October, 1949, the American Academy of Ophthalmology and Otolaryngology conferred an Honorary Fellowship and an Award of Merit upon Sir Stewart Duke-Elder, who was their "Guest of Honour" at this meeting. During the following week he also received the Honorary Fellowship of the American College of Surgeons.

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The American Ophthalmological Society

The American Ophthalmological Society elected new officers at its recent meeting at Hot Springs, Virginia:—*President*, Dr. Parker Heath, Boston; *Vice-President*, Dr. John H. Dunnington, New York; *Secretary-Treasurer*, Dr. Maynard C. Wheeler, New York.

The 1949 Transactions of the American Ophthalmological Society published in book form may be purchased by advance subscription. This volume contains the scientific papers given at the Annual Meeting, and the thesis for membership. Price $12.00. Order from the Editor: Dr. Wilfred E. Fry, 1930 Chestnut Street, Philadelphia, Pa. Orders must be in by December 1.

* * * *

National Society (U.S.A.) for Prevention of Blindness

The next annual conference of the National Society (U.S.A.) for the Prevention of Blindness will be a combined meeting with the Pan-American Association of Ophthalmology, and will be held March 26 to 30, 1950, at the Hotel Floridian, Miami Beach, Florida.

Among the topics to be discussed at the conference are current blindness prevention programmes in the countries of the Western Hemisphere, trachoma, industrial ophthalmology, eye problems of school children, medical and social management of the glaucomas.

The conference is open to all interested persons, and the Executive Director is Franklin M. Foote, M.D., National Society for the Prevention of Blindness, 1790 Broadway, New York 19, N.Y.

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